Review Article

Recent Development in Floating Drug Delivery System: A Review

Beena Kumari

Lecturer in Pharmaceutics
Department of Pharmaceutical Education and Research,
Bhagat Phool Singh Mahila Vishwidylaya, South campus, Bhainswal Kalan, Sonepat, Haryana, India.

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Abstract

In the Gastroretentive drug delivery system (GRDDS), the dosage form that after oral administration retained in the stomach and release the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. In the gastric region, gastro retentive dosage form can remain for several hours and prolong the gastric residence time of drugs significantly. While, the bulk density in floating drug delivery system (FDDS) is more than the gastric fluids and therefore, they remain buoyant in the stomach for a long-time period without affecting gastric emptying rate. When the system is floating on the gastric fluid; the drug releases slowly. This results in an increased gastric residence time and a good control of the rise and fall in plasma drug concentration. For local action in the upper part of the small intestine i.e. treatment of peptic ulcer disease, longer residence time in the stomach could be advantageous. Moreover, drugs that are absorbed readily upon release in the GI tract, improved bioavailability is expected by slow release in the stomach. By the simultaneous administration of pharmacological agents, the controlled gastric retention of solid dosage forms may be achieved that delay gastric emptying or it may be achieved by the mechanisms of sedimentation, flotation, muco-adhesion, expansion, modified shape systems. The main purpose of this paper is to review the concept of gastroretentive drug delivery systems with the recent literature and current technology used in the development of this system.

Keywords: Gastroretentive Floating drug delivery system, Gastric Residence Time

Introduction

Oral route is most preferred, favoured, promising and versatile route for administration of drugs in systemic action. Gastro retentive drug delivery system (GRDDS) is novel site specific drug deliveries to promoting retention with in the stomach, duodenum or small intestine can prolong drug released to controlled manner. The oral administration approaches to achieve prolong release of drug is the use of gastro-retentive systems. The idea is to prolong the residence time of the drug delivery in the stomach known as Gastric Residence Time (GRT) (Chuch et al., 1995).

Oral drug delivery systems (Sharma et al., 2011)

The most common and suitable route for various drugs is oral route. This route usually considered as perfect drug delivery system because of these two main properties:

- Prolonged action with a single dose.
- Directly deliver the drug to the target site.

Important characteristics of oral drug delivery systems (Chuch et al., 1995)

- Broad range of applications which includes local or systemic, food, cosmetic and pharmaceutical products.
- Non-invasive mode of administration.
- Suitability for paediatric/geriatric patients.
- Substantial improvement of patient compliance and convenience.
- Versatile drug release (immediate/extended).
- Customized colour, shape, dimension and taste.
- Cost-effectiveness.

Physiology of the Gastrointestinal Tract (GIT) (Ami et al., 2012; Vishal et al., 2013; Shailaja et al., 2016)

The organ of the body stomach; consist of three sections:

*Address for Corresponding Author:
Beena Kumari
Lecturer in Pharmaceutics
Department of Pharmaceutical Education and Research,
Bhagat Phool Singh Mahila Vishwidylaya, South campus, Bhainswal Kalan, Sonepat, Haryana, India.
E-mail: beenasangwan051119993@gmail.com
Mobile n: 9992185034

Body, antrum (pylorus) and fundus, with a capability for storage and mixing. The central part for mixing motions is antrum whereas the body part and fundus act as a reservoir for undigested material. And for gastric emptying by propelling actions, the antrum acts as a pump (Figure 1). Under fasting conditions with a residual volume of approximately 50 ml the stomach is identical to a collapsed bag and also contains a small volume of gastric fluid having pH 1 to 3. The mucus covers the mucosal surface of the stomach and the rest of the GI tract. The GI tract comprising of two modes, one is digestive motility pattern and the other another is interdigestive motility pattern is in a state of constant motility. As in the fasted state, cleaning up the residual content of the upper GIT is a primary function so the former is dominant. Controlled cycles of activity and dormancy in the interdigestive motility pattern are usually known as migrating motor complex (MMC) (Meenakshi et al., 2015).

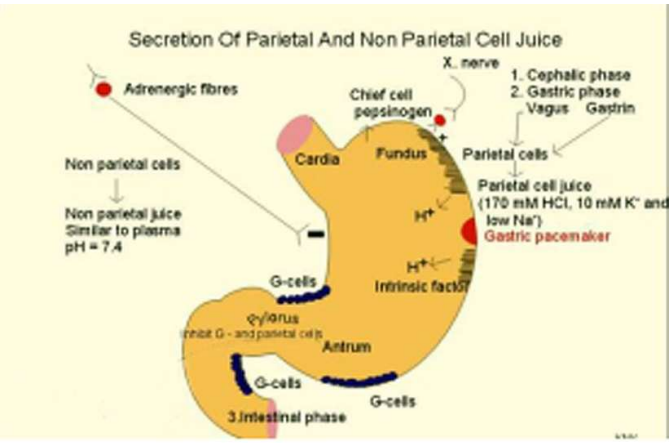

Figure 1. Physiology of Stomach (Meenakshi et al., 2015)

Both during fasted and fed states, the process of gastric emptying occurs however the pattern of motility differs during fasted and fed states. The fasted state is characterized by intra gastric series of electrical events. This activity is called migrating motor complex (Figure 2) which occurs both through intestine and stomach every 2-3 h. It is further divided into four consecutive phases as:

Phase 1: It is dormant period long-lasting from 40-60 min with unusual contractions.

Phase 2: It continues for about 40-60 min and consists of spasmodic action potentials and contractions which regularly increase in frequency and intensity.

Phase 3: This is a smaller duration of intense, large steady proximal and distal contractions lasting from 4 to 6 min, and called *'house-keeper wave'* since from stomach to intestine it sweeps undigested gastric contents.

Phase 4: A short-term transitional phase about 0-5 min that occurs between two consecutive phases i.e. phase 1 and phase 3.

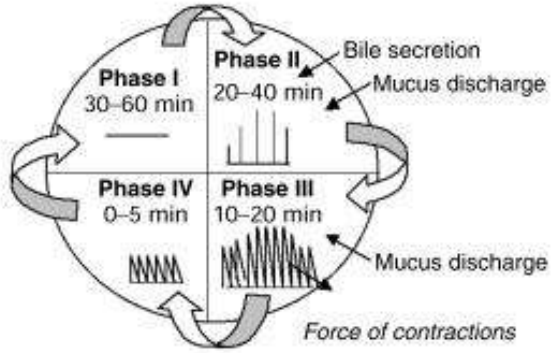

Figure 2. Motility Patterns of the GIT in the Fasted State (Meenakshi et al., 2015)

This cycle after feedings leads to changes in array of contractions known as digestive motility pattern which may last for many minutes. It comprises of continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to < 1 mm), which are propelled toward the pylorus in a suspension form. In the fed state, the gastric emptying rate (GER) is slow down because the start of migrating motor complex is delayed.

In the fasted state, when controlled release drug delivery system (CRDDS) are directed, the migrating motor complex may be in any of its stages, which can affect the total GRT and transit time in the GIT. The lower the degree of absorption when the less time spent in that region. Therefore, the resistance of the dosage form to gastric emptying during Phase III of the migrating motor complex in the fasted state in the design of GRDDS should be take into concern and also to continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS must be efficient after administration and able to resist the invasive of physiological events for the required period of time (Meenakshi et al., 2015).

Approaches to Gastric Retention (Meenakshi et al., 2015)

a) Floating drug delivery systems (FDDS)

b) Bio adhesive systems

c) High density systems

d) Swelling and expandable systems

e) Ion exchange resins systems

Floating drug delivery systems (FDDS)

The bulk density of these systems is more than the gastric fluids and therefore, without affecting gastric emptying rate they remain buoyant in the stomach for a long time period. When the system is floating on the gastric fluid, the drug releases occurs slowly. The residual system is emptied from

the stomach when drug is released. This results in an increased gastric residence time and a good control of the rise and fall in plasma drug concentration (Bansal et al., 2003). Drug Release Profile Showing the differences between zero-order controlled release and sustain release are shown in figure 3.

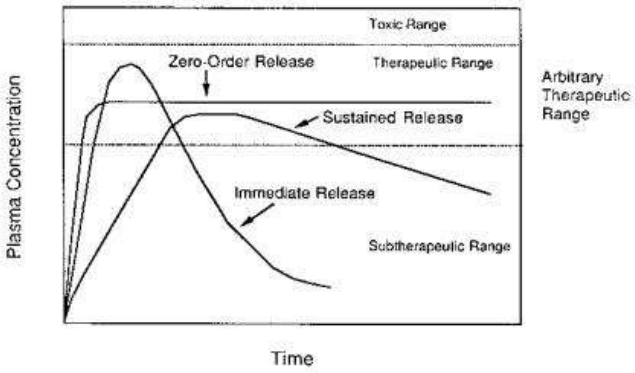

Figure 3. Drug Release Profile Showing the Differences Between Zero-Order Controlled Release(Bansal et al., 2003)

Bioadhesive or mucoadhesive systems

To define an interaction between the mucin layer that lines the entire GIT and a bioadhesive polymer the term '*mucoadhesion*' is commonly used. Within the lumen to enhance drug absorption in a site specific manner bioadhesive drug delivery systems (BDDS) are used as a delivery device. The use of bioadhesive polymers involves by this system, which can adhere to the epithelial surface in the stomach. Thus, they prolong the gastric retention time (Meenakshi et al., 2015).

High density systems

This approach includes formulation of dosage forms with the density that must be more than density of normal stomach content (~ 1.004 gm/cm^3). By coating drug on a heavy core or mixed with inert materials, this type of formulations are prepared. The inert materials used are such as barium sulphate, iron powder, zinc oxide and titanium oxide etc. The density of materials increases up to 1.5- 2.4 gm/cm^3. A density near to 2.5gm/cm^3 seems necessary for significant prolongation of gastric residence time (Nayak et al., 2012).

Swelling and expanding Systems

Since this system exhibit tendency to remain logged in the pyloric sphincters so called as "*Plug type system*". Even in fed state, these polymeric matrices remain in the gastric cavity for several hours (Arrora et al., 2015).

Ion-exchange Resins

A coated ion exchange resin which was loaded with bicarbonates have gastric retentive properties. A negatively charged drug is bound to the resin after them loaded with bicarbonate and to overawe the quick loss of carbon dioxide, resultant beads were then encapsulated in a semi permeable membrane. An exchange of bicarbonate and chloride ions take place upon onset in the acidic environment of the stomach. For carrying beads towards the top of gastric content, CO_2 was released and trapped in a membrane. In contrast the uncoated beads a floating layer of resin beads is produced, which will sink quickly(Garg and Gupta, 2012). And various approaches to gastric retention are shown in figure 4.

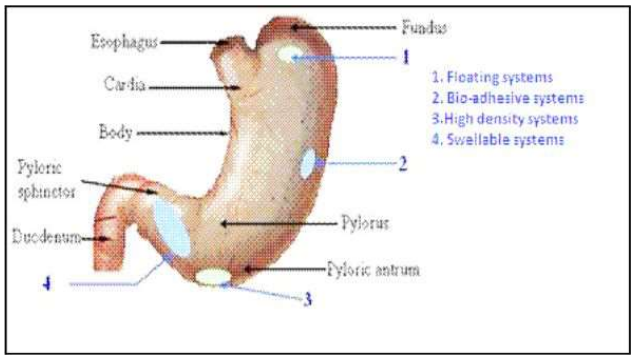

Figure 4. Approaches to Gastric Retention (Chaturvedi et al., 2013)

Different Approaches to Design FDDS

There are two different approaches to design FDDS. These two are (a) Single unit FDDS and (b) Multi-unit FDDS

Single unit FDDS

Effervescent substances are incorporated in the hydrophilic polymer and CO_2 bubbles are trapped in the swollen matrix in single unit systems e.g., bilayer systems. But due to the problems such as sticking to each other or obstruction to GIT these formulations may result in local irritation. "*All or none*" phenomenon is the main drawback of such systems. 'But there is risk of the dosage form passing into intestine when of house keeper waves are produced, in such cases (Pande et al., 2013).

Multiple unit FDDS

This type of system consists small discrete units, each exhibiting some desired characteristics and multiplicity. The active substance is present as a number of small independent sub units in these pharmaceutical formulations. "*All or none*" gastric emptying nature of single unit systems avoided multiple unit systems. It reduces the inter subject variability in absorption and the probability for dose dumping is lower, e.g. floating microspheres(Narang, 2011).

Types of FDDS

- Effervescent Systems (Gas-generating systems)
  - Gas generating systems
  - Volatile liquid containing systems

➢ Non-effervescent Systems

• Hydrodynamically balanced systems or Colloidal gel barrier systems

• Microporous compartment systems

• Alginate beads systems

• Hollow microspheres systems

➢ Raft Forming Systems

Effervescent FDDS

The matrix type systems containing effervescent components like sodium bicarbonate, citric acid, tartaric acid and calcium carbonate and also swellable polymers such as polysaccharides or hydroxy propyl methyl-cellulose (HPMC) and chitosan. When these dosage forms interact with gastric juice in the stomach, trapped in the swollen hydrocolloids and CO_2 liberated. This provides buoyancy to the dosage form (Meenakshi et al., 2015 and Goyal et al., 2011). These buoyant delivery systems are prepared with swellable polymers such as methocel, polysaccharides, e.g. chitosan and various effervescent components, e.g. sodium bicarbonate. Different approaches used in effervescent floating drug delivery system (EFDDS) are:

Gas generating systems (Arunachalam et al., 2011)

These buoyant systems utilized matrices prepared with effervescent constituents i.e. $NaHCO_3$ citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature and swellable polymers like HPMC, poly saccharides i.e. chitosan. For gas generation the optimal stoichiometric ratio of citric acid and sodium bicarbonate is reported to be 0.76:1. Excipients including HPMC, agar, poly acrylate polymers, polyvinyl acetate, Carbopol®, sodium alginate, poly ethylene oxide, calcium chloride and polycarbonates are used most commonly in these systems (Chandel et al., 2012). Drug release from effervescent (Gas Generating) systems is shown in figure 5.

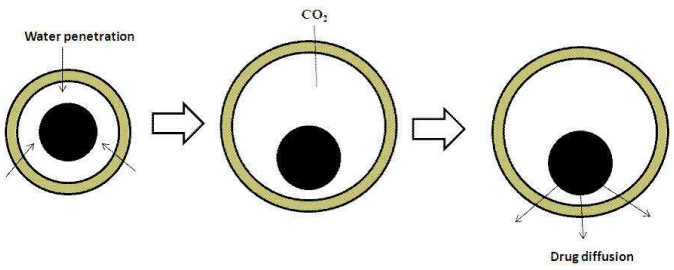

Figure 5. Drug Release from Effervescent or Gas Generating Systems (Chandel et al., 2012)

Volatile liquid containing systems

By incorporating an inflatable chamber, the gastric residence time of a drug delivery system can be sustained which contains a liquid i.e. cyclopentane and ether, and gasifies at body temperature to cause the inflation of the compartment in the stomach. As shown in figure 6, the device also consist a bio-erodible of Polyethylene, PVA etc. that steadily dissolves and causing the inflatable compartment to release gas and after a predetermined time collapse to permit the spontaneous expulsion of the inflatable systems from the stomach (Meenakshi et al., 2015; Kumar et al., 2012).

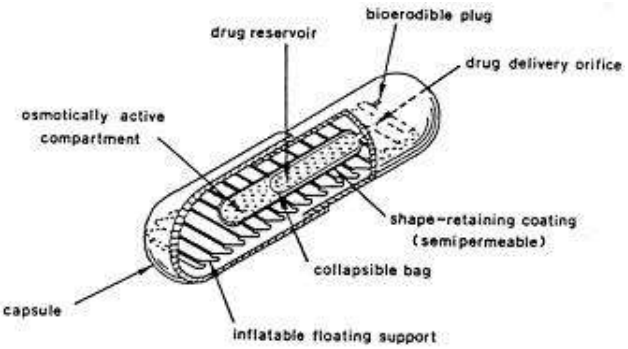

Figure 6. Volatile Liquid Containing System (Meenakshi et al., 2015)

Non-effervescent FDDS

The most commonly used polymers for the preparation of these systems are gel forming or highly swellable type or matrix forming type. Highly swellable polymers used are such as polysaccharides, hydrocolloids and matrix forming polymers are like polyacrylate, polymethacrylate, polycarbonate and polystyrene. The approach of this type of formulation includes mixing of drug with a gel forming hydrocolloid, which swells after oral administration in contact with gastric fluid and reaches a bulk density of less than unity. Buoyancy to the dosage form attained by trapping air within the swollen polymer matrix. This system comprises further sub-types (Mayavanshi and Gajjar, 2008).

• Hydrodynamically balanced systems or colloidal gel barrier systems

• Microporous compartment systems

Hydrodynamically balanced systems (HBS) or colloidal gel barrier systems

The system as shown in figure 7, in the stomach content containing gel-forming hydrocolloids with a drug intended to remain buoyant. The amount of drug maximizes in this system which prolongs the GRT to reach at its absorbtion sites in the solution form for the complete absorption. A high level of one or more gel-forming highly soluble cellulose and matrix-forming polymer are incorporated in this system. Gel-forming highly soluble cellulose type hydrocolloid used are i.e. hydoxyethyl cellulose, polysaccharides, hydroxyl propyl methyl cellulose (HPMC) and hydroxyl propyl cellulose and the matrix-forming polymer used are such as polystyrene, polyacrylate

and polycarbophil (Meenakshi et al., 2015, Garg and Gupta 2012).

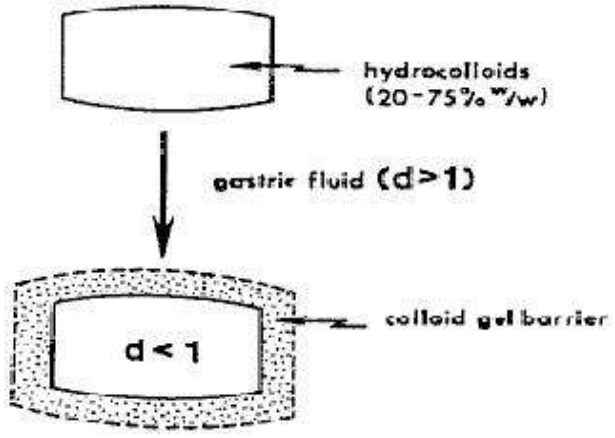

Figure 7. Hydrodynamically Balanced System(Meenakshi et al., 2015)

Microporous compartment systems

This system consist as shown in figure 8, in a microporous compartment which is having pores on both surfaces i.e. top and bottom encapsulated a drug reservoir within it. To remain the undissolved drug free, the peripheral walls of the reservoir compartment were completely sealed. Based on unfolding polymeric membranes novel levodopa gastro retentive dosage form is used which combines extended dimensions with high rigidity. A large size gelatin capsules may be formed using this system. *In vitro* studies showed that after administration, the unfolded form reached within 15 mins and using beagle dogs it was also confirmed *in vivo*. For at least 2 hours the unfolded form was maintained. It was concluded that therapy of different narrow absorption window drugs could be improved by using this system (Nadigoti and Shaveda, 2009).

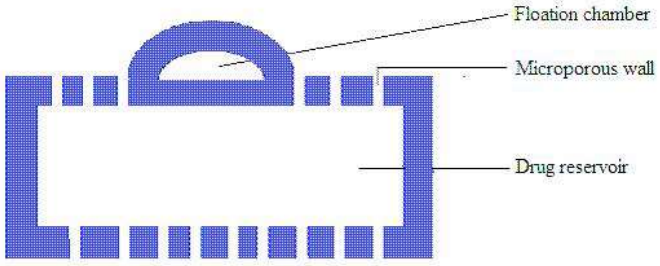

Figure 8. Microporous Compartment Systems (Meenakshi et al., 2015)

Alginate beads

These beads have been developed from freeze-dried calcium alginate and are multi-unit floating dosage forms. Into aqueous solution of calcium chloride, by dropping sodium alginate solution causing the precipitation of calcium alginate these can be prepared. In this phenomenon spherical beads having diameter of approximately 2.5 mm are formed. Polymers used to develop these systems are such as low methoxylated pectin, cellulose acetate, polycarbonate, calcium alginate, Eudragit and agar (Ami et al., 2012).

Hollow microspheres

Hollow microspheres are considered as one of the most favourable buoyant systems. Due to central hollow space within the microsphere which enhanced floating properties the system have main advantages of multiple unit systems. The techniques for their preparation includes solvent diffusion and evaporation or simple solvent evaporation. Floating hollow microsphere or microballoon are as shown in figure 9. The good floating properties and drug release depend on the type of plasticizer, polymer and the solvents employed for the preparation(Garg and Gupta, 2012).

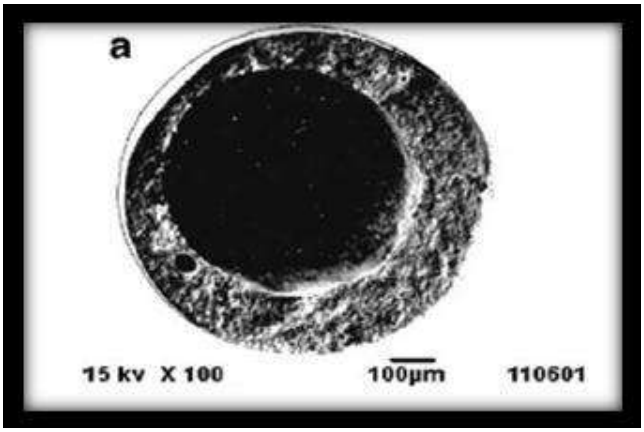

Figure 9. Floating Hollow Microballoon or Microsphere **(**Garg and Gupta, 2012)

Raft forming system: A gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells, in contact with gastric fluid and containing entrapped CO_2 bubbles forms a viscous cohesive gel. On the top of gastric fluid this gel forms raft layer which releases the drug slowly into the stomach. These type of formulations to reduce gastric acidity contains antacids i.e. aluminium hydroxide or calcium carbonate (Patel et al., 2012). Schematic Illustration of the barrier formed by a Raft-Forming System is shown in figure 10.

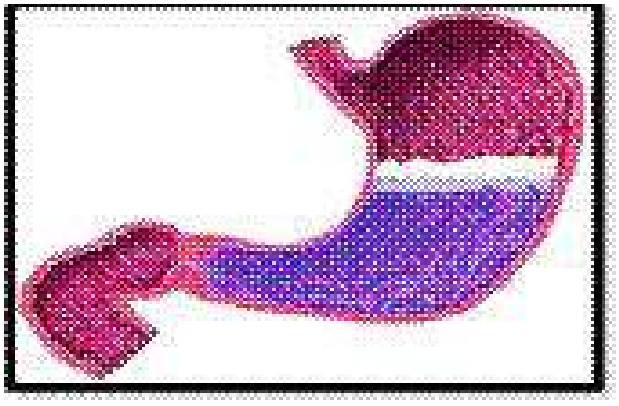

Figure 10. Schematic Illustration of the Barrier Formed by a Raft-Forming System (Meenakshi et al., 2015)

Table 1. Some of the Marketed Gastro Retentive Formulations(Sharma et al., 2011)

S. No.	Brand Name	Type/Drug	Manufacturer	Uses	Remarks
1.	Madopar	Floating capsule, Levodopa and benserzide	Roche, USA	Peripheral dopa decarboxylase inhibitor	Floating, CR Capsule
2.	Valrelease	Floating capsule, Diazepam	Hoffmann-LaRoche, USA	Tranquilizer	Floating capsule
3.	Topalkan	Floating Antacid, Aluminium Magnesium Antacid	Pierre Fabre Drug, France	Antacid, antiseptic, and protective	Floating liquid alginate preparation
4.	AlmagateFlot-coat	Floating Antacid	Roche, USA	Antacid	Floating dosage form
5.	Liquid gaviscon	Floating Gel, Alginic acid and sodium bicarbonate	Glaxo Smith Kline, India	Suppress gastro-esophageal reflux and alleviate the heart burn	Effervescent floating liquid alginate preparation

The aim for designing controlled floating delivery system to increase effectiveness of drug by localization at the site of action and/ or to reduce the frequency of dosing or reducing the dose required or providing uniform drug delivery with high bioavailability of buoyant drugs. Many marketed formulations are there as shown in Table 1.

Factors Affecting the FDDS (Meenakshi et al., 2015, Shailaja et al., 2016 and Ami et al., 2012)

Density: Gastric retention time is mainly depends on the density.

Size: Diameter of dosage form units 9.9 mm compared with those with a diameter of more than 7.5 mm are reported to have less gastric residence time.

Shape of dosage form: With the shapes tetrahedron and ring shaped devices comparison is done with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported.

Single (or) multiple unit formulation: Due to failure of units, multiple unit formulations show minor impairing of performance.

Nature of meal: Feeding of fatty acid and indigestible polymers by reducing the GRT and prolonging drug release can alter the motility pattern of the stomach to a fed state.

Caloric content: With a meal that is high in proteins and fats gastric residence time can be increased by 4 to 10 h.

Frequency of feed: When successive meals are given the GRT can increase by 400 min, compared with a single meal due to the low frequency of MMC.

Gender: Mean ambulatory gastric residence time in males is less when compared with females. In male it is 3.4 ± 0.6 h while in females it is 4.6 ± 1.2 h, irrespective of the weight, height and body surface.

Age: People, especially those over 70 years, have a significantly longer gastric residence time.

Posture: Gastric residence time can differ between supine and upright ambulatory states of the patient.

Concomitant drug administration: Anti-cholinergics like propantheline and atropine, opiates like codeine and prokinetic agents like cisapride and metoclopramide; can affect floating time.

Advantages of FDDS (Brahmankar and Jaiswal, 2006)

- Enhances the bioavailability and therapeutic efficacy of drugs with narrow absorption window in the upper part of GIT.
- Retaining the dosage unit in the stomach for prolonged period of time.
- Site specific drug delivery improves local therapy in the GIT by increasing gastric residence time, thus improved systemic absorption and less premature drug degradation.
- Fluctuations are minimized due to continuous input of the drug.
- Minimizes or eliminates the side effects by delivering the drug at the active site.
- This system is advantageous in case when there is dynamic intestinal movement and a shorter transit time as might occur in certain type of diarrhoea, which results less absorption.

Table 2. Floating Drug Delivery Products Available in the Market (Shakti and vikash, 2011)

Brand Name	Active ingredient	Clinical Importance
Cifran OD ®	Ciprofloxacin	Urinary tract infection
Madopar ®	L-DOPA and Benserazide	Parkinsonism
Valrelease ®	Diazepam	Sedative –Hypnotic
Topalkan ®	Aluminum -magnesium antacid	Antacid
Liquid Gavison ®	Aluminium hydroxide	Heart burn
Conviron	Ferrous sulphate	Pernicious anaemia
Cytotec®	Misoprostol	Gastric Ulcer

- Prolongation of the total GI transit time reduces the number of doses in the regimen which improves patient compliance

Disadvantages of FDDS (Shailaja et al., 2016 and Dwivedi and Kumar, 2011)

- Require high volume of fluids in the stomach.
- For drugs that may cause gastric lesions e.g. NSAIDS is not suitable.
- The floating systems in patients with achlorhydria can be questionable in case of swellable system.
- In the stomach residence time depends upon the digestive state.
- The hydration state of the dosage form shows the ability to float. Spasmodic administration of water (a tumbler full, every 2 h) is favourable to keep these tablets floating *in vivo*.
- Drug like Nifedipine cannot be formed as FDDS because the slow gastric emptying may cause reduced systemic bio-availability.

Drugs Selected for FDDS(Sarojini and Manavalan, 2012)

- Drugs acting locally e.g. drugs for *H. pylori* viz., Misoprostol and Antacids in the stomach
- Predominantly absorption of drug in the stomach e.g. Amoxicillin.
- Drugs which are less soluble at alkaline pH i.e. Diazepam, Furosemide and Verapamil etc.
- Drugs which are absorbed rapidly from the GI tract e.g. Metronidazole, tetracycline.
- Drugs that degrade in the colon e.g. Ranitidine, Metformin HCL.

Drugs Unsuitable for FDDS(Sarojini and Manavalan, 2012)

- Drugs having low solubility in acidic environment i.e. phenytoin etc.
- Drugs which are instable in the gastric medium i.e. erythromycin etc.
- Drugs proposed for selective release in the colon i.e. 5-aminosalicylic acid and corticosteroids etc.

Applications of Floating Drug Delivery Systems (FDDS) (Ami et al., 2012 and Nayak et al., 2012)

- Due to increased gastric residence time, FDDS is useful in treatment of gastric ulcer.
- For maintaining desired plasma level of drugs, floating granules of Indomethacin.
- In treatment of hypertension, recent studies conferring the diltiazem floating tablet are more active as compared to conventional tablet.
- Due to prolonged gastric residence time, it is used to destroy *H .pylori*, causative organism for peptic ulcer and chronic gastritis.
- In treatment of stomach neoplasm, i.e. 5-fluorouracil.

Marketed Products of FDDS

In the market there are many products of FDDS. These formulations are having clinical importance. Some products are shown in Table 2.

Selection of the Suitable Drug Candidate and Other Excipients

Desirable properties of the drug candidate for FDDS are (Sarojini and Manavalan, 2012)

- Drug should have site specific absorption e.g. in stomach.
- The dose of drug should be small.
- Aqueous solubility of drug should be limited.
- Partition coefficient should be balanced.
- Drug should be stable in the GIT and biological half-life should be short.
- Therapeutic index should be high.

Future potential (Sanjay et al., 2009)

- As evident from several recent publications floating dosage form offers various future potential. The fluctuations in the plasma level of drug are reduced and results in delayed gastric emptying.

- Many drugs due to their limited absorption to the upper gastrointestinal tract have poor bioavailability; can be delivered efficiently in this type of dosage form and thereby maximizing their absorption and improving their absolute bioavailability.
- For the treatment of gastric and duodenal cancers buoyant delivery system considered as a beneficial strategy.
- In the development of various antireflux formulations the floating concept can also be utilized.
- By using the narrow spectrum antibodies the eradication of Helicobacter pylori can be explored.

Conclusion

GRDDS is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper GI tract improving the oral sustained delivery of drug that have an absorption window in a particular region of the GI tract. These systems ensure optimal bioavailability and before the drug reaches the absorption window it helps in continuously releasing the drug. At the particular sites of absorption it provides continuously controlled release administration of sparingly soluble drugs and thus this manner may increase patient compliance. Presently, more than 55% of drug available in the commercial market as orally administration.

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