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FLOATING DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW AND ITS POSSIBLE SCOPE

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ABSTRACT

In our day to day life oral dosage forms are known to be superior because of its advantages. Furthermore new Oral sustained release dosage forms (SRDFs) have been developed; however, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the Gastrointestinal tract (GIT), the drug gets released in distal segments of the GIT which results in a short absorption phase that is often accompanied by lesser bioavailability. It was suggested that compounding narrow absorption window drugs with gastroretentive properties would enable an extended absorption phase of these drugs. New trends in GRDDS to increase the duration of oral dosage form in the stomach, includes floating systems, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices. Floating systems have bulk density lower than that of the gastric fluid and remain buoyant in stomach for prolong period. After oral administration; such a dosage form would be retained in the stomach and release the drug in a sustained manner, so that the drug could be supplied continuously to its absorption sites in the upper GIT. This mode of administration would provide the known pharmacokinetic and pharmacodynamics of SRDFs for such drugs; in this overview, types of floating system, factors affecting gastric retention, evaluation of floating system have been discussed.

Key words: Bioavailability, Floating, Gastric retention time, Sustained release dosage forms.

INTRODUCTION

Now a days as pharmaceutical scientists acquire a better understanding of physicochemical and biological parameters of drugs delivery, maximizing the therapeutic index of the drug and reduction in the side effects become sophisticated. In All over drug delivery systems, still the oral drug delivery is the mainstay of treatment due to patient compliance and low patient discomfort.

Despite tremendous advancement, the oral route remains the preferred route of administration because of low cost of therapy and high level of patient compliance. More than 50% of drug delivery is available as oral drug delivery. Further novelty i.e. controlled release of drug ideally enables the drug release at predetermined and controlled rate [1]. But unfortunately this ideal therapeutic target cannot be achieved systemically due to inter & intra subject variability of GI transit time and from non-uniformity of drug absorption throughout the alimentary canal. Drugs having site specific absorption are difficult to design as oral Controlled release dosage form, because only the drug released in the region proceeding and in close vicinity to the absorption window is available for absorption. The released drug goes into waste with negligible or no absorption. Under certain circumstances prolonging the gastric retention of a drug delivery system is desirable for achieving greater therapeutic benefit of the drug. Thus all these limitations can be overcome by increasing the gastric residence time of dosage form i.e. the development of GRDDS (gastro retentive drug delivery system).

Dosage forms that can be retained in the stomach for prolonged and predictable period are called as gastroretentive drug delivery system. Therefore the real issue in developing GRDDS is not just to prolong the delivery of drugs for more than12 hr. but to achieve presence of drug delivery system in stomach or upper GIT until the entire drug is released. Thus, GRDDS can improve the controlled delivery of drug that have an absorption window by continuously releasing drug for

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prolonged period of time before it reaches to absorption site. Over past few decades various attempts have been made to develop GRDDS as floating, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices(as magnetic systems, super porous biodegradable hydrogel systems etc). These benefits to the drugs that have narrow absorption window.

Basic anatomy & physiology of stomach

Anatomically stomach is a J-shaped and having the three major parts that are: fundus, body, and antrum (pylorus). The proximal part made of fundus and body, acts as a container for undigested material, whereas the antrum serves as propeller for gastric emptying actions. Under fasting conditions, the stomach is filled with a residual volume (of approximately 50ml) and contains a small amount of gastric fluid (pH 1– 3) and air. The mucus cells secrete alkaline mucus that covers all the epithelium and protects it from acid of the stomach. Parietal cells secrete hydrochloric acid where chief cell secretes proteolytic enzyme pepsin. The GIT is in 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 GIT. The interdigestive motility pattern is commonly called the 'Migrating Motor Complex' ('MMC') and is organized in cycles of activity and quiescence. Each cycle lasts for 90–120 minutes and consists of four phases. Duration of the phases is controlled by the concentration of hormone. In the interdigestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower oesophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum [2, 3].

Four phases of GI motility

1. **Phase I** (basal phase) – It occurs for 40 to 60 minutes with rare contractions.
2. **Phase II** (pre-burst phase) –It lasts for 40 to 60 minutes with action potential and contractions. With the phase progression the intensity and frequency also Increases gradually.
3. **Phase III** (burst phase) – It occurs for 4 to 6 minutes. It includes intense and regular contractions for short period. Because of this all the undigested material is passed out of the stomach down to the small intestine. Burst phase also known as the Housekeeper Wave.
4. **Phase IV** – It is for up to 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

Requirements of gastric retention

It must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic movement in the stomach and the constant contractions and grinding mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease[4].

Drug candidates for GRDDS

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) e.g. Levodopa, Riboflavin.
- Less soluble drugs or Drugs which get degraded by the alkaline pH which they encounter at the lower part of GIT e.g. Furosemide, Verapamil.
- Drugs that are absorbed due to variable gastric emptying time. Local sustained drug delivery to stomach and proximal small intestine to treat certain conditions particularly for the treatment of peptic ulcers caused by *H. Pylori* infections.
- Drugs that get degraded at colon pH e.g. ranitidine, Metformin HCL [5].

Advantages of floating drug delivery

1. Improved patient compliance.
2. Controlled and prolonged release of drug.
3. Ease of manufacture with simple equipment.
4. Improved patient compliance.
5. Local delivery of drug to stomach.
6. Minimizes gastric irritation by slow and controlled release of drug.
7. Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. b-lactam antibiotics (penicillin & cephalosporin) [5,6].

Limitations

1. In few situations where gastric retention is not desirable. Aspirin and NSAID are known to cause G.I. lesions & slow release of such drug in stomach is unwanted.
2. These systems require the presence of food to delay their gastric emptying.
3. Floating systems require high levels of fluids in the stomach.
4. It is not suitable for drugs which are unstable at Gastric pH [7].

Factors Affecting Gastric retention

1. Density: Gastric retention time (GRT) is a function of dosage form buoyancy. With low density better buoyancy can be achieved.
2. Size: Dosage forms with a diameter of more than 7.5mm have an increased GRT compared with those with a diameter of 9.9mm. Above 9.9mm diameter devices also show increased GRT.
3. Shape of dosage form: Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (kpsi) have better floating properties up to 24 hours.
4. Single or multiple unit formulation: Multiple unit formulations show a better release profile and performance than the single unit formulations.

5. Fed or unfed state: Under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs after every 1.5 to 2 hours. This complex sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the Gastric retention time of the unit can be Very short. However, after meals MMC is delayed and Gastric retention time is prolonged.
6. Nature of meal: Change in motility of stomach may occur after Feeding of indigestible polymers or fatty acid salts, thus decrease the gastric emptying rate and prolonged drug release can be expected.
7. Caloric content: Gastric retention time can be increased by 4 to 10 hours after intake of high protein and fat content.
8. Frequency of feed: Gastric retention time can increased over 400 minutes, upon successive meals due to the low frequency of MMC.
9. Gender: In males (3.4±0.6 hours) Gastric retention time is less compared with female (4.6±1.2 hours), regardless of the weight, height and body surface.
10. Age: Elderly people, especially those over 60, have a significantly longer Gastric retention time [8].

Strategies for Gastro retentive drug delivery system
Swelling/expandable type GRDDS

This type of dosage form is such that after swelling, this product swells to extent that prevents their exit from the stomach through the pylorus. As, a result, the dosage form get retained in the stomach for a longer period of time. Swelling usually occurs due to osmosis. These systems may be referred to as a "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. Unfolding takes place due to mechanical shape memory [9].

Arza RA *et al.,* formulated swellable and floating gastroretentive ciprofloxacin hydrochloride tablet using combination of HPMC and crosspovidone, CMC [10].

Revathi S, Natarajan R *et al.,* optimized and evaluated Ciprofloxacin swellable floating matrix tablet on gastric residence time with varying concentration of excipients [11].

Bioadhesive or mucoadhesive systems

They 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 approach involves the use of bioadhesive polymers that can be adhering to the epithelial surface of the GIT. The proposed mechanisms for this system are an interaction based on hydration mediated, receptor mediated or bonding mediated adhesion with the biological membrane of the gastrointestinal mucosa. Some promising excipients that have been used are carbopol, chitosan, polycarbophil, lectins etc.

Magnetic systems

In this system, dosage form contains a small internal magnet and magnet is placed on abdomen over the position of stomach. Although these systems seem to work the external magnet must be positioned with degree of precision that might compromise patient compliance [12].

Raft systems In this system, swelling of gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) takes place and it forms a viscous cohesive gel containing entrapped CO_2 bubbles on contact with gastric fluid. Formulations are also typically used for antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. The mechanism of the raft forming system involves the formation of continuous layer called a raft. The system involves the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The layer of the gel floats on the gastric fluid because it has bulk density less than the gastric fluid, as low density is created by the formation of CO2. So the system remains buoyant in the GIT [**[**13**,**14].

Floating drug delivery system: Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for prolong period [15]. Floating drug delivery systems are classified depending on the use of two formulation variables:
1. Effervescent systems.
2. Non-effervescent systems.

Effervescent buoyant system
Volatile liquid containing systems

The Gastric retention time of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach developed.

This layer was further divided into two sub layers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of polyvinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. It was shown that the swellable membrane layer played an important role in maintaining the buoyancy of the pills for an extended period of time.

Gas-generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2[16], which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

Swati Jagdale *et al.,* studied the effect of gas forming agents on floating drug delivery of tramadol hydrochloride. The 1:1 ratio of effervescent couple had shown better floating of dosage form for 24 Hrs [17].

Non-effervescent systems

Colloidal gel barrier systems

Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporates a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, sodium-CMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

Micro porous Compartment System

This technology is based on the encapsulation of drug reservoir inside a micro porous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption [18].

Alginate beads multiple unit floating dosage forms have been developed from freeze-dried calcium alginate [19]. Spherical shaped beads of approximately 2.5 mm in diameter can be prepared by adding sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen using liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can show a floating force over 12 hours.

Tripathi G *et al.,* Formulated and evaluated pH sensitive oil entrapped polymeric blended gellan gum buoyant beads of clarithromycin[20] using above system.

Evaluation of floating dosage form

A) *In-vitro* evaluation[21]

1. Buoyancy lag time - In order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium, can be measured using dissolution test apparatus.

2. Floating time and in-vitro drug release - Can be determined using USP II apparatus stirring speed at 50 rpm at 37+/-2^{0}C in stimulated gastric fluid pH 1.2.the samples are collected and analysed for the drug content. The time for which dosage form remains buoyant on the surface of dissolution medium is floating duration.

3. Swelling index: The swelling ratio Qs can be expressed by ability of polymer to absorb water and can calculated using the following equation.

$Q_s = W_s - W_d / W_d$

Where,

W_d = is the is the weight of the bead dry state

W_s = the weight in the swollen state.

B) *In-vivo* evaluation [22]

This is carried out by means of X-ray or Gamma scintiography monitoring of the dosage form transition in the GIT.

RESEARCH ENVISAGED

Pharmaceutical research has gained a milestone by providing various novel alternatives to the conventional drug dosage system. With the introduction of new polymers and excipients there has been a constant up gradation of drug delivery system to impart benefits to patients. Recently, there has been lot of work in the investigations related to the use of different pharmaceutical technology for oral drug delivery system as controlled drug delivery matrices. Gastroretentive drug delivery system is one of the promising approach for oral controlled drug delivery which allows the drug to retain in the stomach and release them in a more reproducible and predictable manner. Various types of drugs with absorption window in stomach and small intestine have been evaluated in developing such delivery system. Also the use of gastroretentive drug delivery system for various different diseases for drug delivery is a part of ever growing research.

Rishad R *et al.,* developed Novel Floating In-situ Gelling System for Stomach Specific Drug Delivery of the Narrow Absorption Window Drug Baclofen. Sodium alginate-based in-situ gelling systems were prepared by using sodium alginate and de-ionized water, to which varying concentrations of drug and calcium bicarbonate were added. The floating lag time and floating time found to be 2 min and 12 h respectively. The drug release from the in-situ gel followed the Higuchi model, which shown a diffusion-controlled release [25].

Kawashia Y, Niwa T *et al.,* developed hollow microspheres for use as a floating controlled drug delivery system in stomach. Hollow microspheres, loaded with Ibuprofen in their outer polymer shells, were prepared by a novel emulsion-solvent diffusion method. In vitro, the microballoons floated continuously over the surface of acidic dissolution media containing surfactant for prolonged time. The drug release behaviour of the microballoons was characterized as an enteric property, and drug release rates were reduced depending on the polymer concentration at pH 6.8 [26].

Muge Kılıçarslan, Tamer Baykara studied the effect of the drug/polymer ratio on the properties of the verapamil HCl loaded microspheres. Drug/polymer ratio was altered while the other formulation parameters were kept constant and percentage yield value, incorporation efficiency,

particle size and distribution of the microspheres were analyzed. Micrographs of the microspheres shown that the variation in drug/polymer ratios might have an influence on the physical characteristics of the microspheres and the increasing amount of polymer might be result in decreased drug dissolve [27].

Md. Ismail Mouzam *et al.,* developed Preparation of a novel floating ring capsule-type dosage form for stomach specific delivery. Objectives were to develop a unique floating ring capsule dosage form which combines gastric soluble and insoluble portions, and to evaluate its suitability for stomach specific drug delivery. In this study effect of polymer concentration, floating behavior was also checked and finally summarized as high amount of HPMC showed prolonged drug release with floating better abilities [28].

Oth M *et al.,* formulated a bilayer floating dosage unit to achieve local delivery of Misoprostal. The system was capsule consisting of a two layers i.e. floating layer maintaining the dosage unit buoyant upon the gastric content and drug layer formulated to act as a sustained delivery system. The differential design of the two layers allows the optimization of both floating capability and drug release profile [29].

Joseph N *et al.,* developed floating, hollow polycarbonate microspheres of piroxicam by solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. It was capable of sustained delivery of the drug over a prolonged period [30].

El-Kamel A *et al.,* designed sustained release system for ketoprofen to increase its residence time in the stomach without contact with the mucosa, which was achieved through the preparation of floating microparticles by the emulsion-solvent diffusion technique. Different concentrations of Eudragit polymer were used to form the floating microparticles. The results indicated that drug retained in the floating microparticles decreased with increase in polymer content [31].

Atyabi F *et al.,* Carried out In-vivo evaluation of novel gastric retention formulation based on ion exchange resins. They prepared ion exchange resins loaded with bicarbonate, which on contact with media containing HCl, release carbon dioxide causing resins to float. They found resin exhibit floating time more than 24 h. with significant prolonged residence time [32].

Dalavi VV *et al.,* studied gastroretentive drug delivery system of an antiretroviral agent. They used Zidovudine compound for the treatment of HIV to enhance its bioavailibity and sustained action. Out of various trial based formulations, the one with good floating time (24hrs) and the percent drug release (98.05) emerged as optimal[33].

Table 1. Few commercial Gastro-retentive Floating formulations [23,24]

Name	Type and Drug	Remarks
MadoparHBSR (PropalHBS)	Floating capsule, Levodopa and benserazide	Floating CR capsules
ValreleaseR34	Diazepam	Floating Capsules
TopalkanR	Floating Antacid, aluminium and magnesium mixture	Effervescent floating liquid alginate preparation
Cifran ODR	Ciprofloxacin (1 gm.)	Gas generating floating Form
Liquid GavisconeR	Mixture of alginate	Suppress gastro oesophageal reflux and alleviate the heart burn
Cytotech	Misoprostol (100 mcg/200mcg)	Bilayer floating capsule
Glumetza	Metformin Hydrochloride	Gas-generating floating tablet

Table 2. Patents for some Floating Gastro-Retentive delivery systems

US patent No.	Patent title
5,972,389	Gastric-retentive, oral drug dosage forms for the controlled release of sparingly soluble drugs and insoluble matter.
5,443,843	Gastric-retention system for controlled drug release.
5,232,704	Sustained-release, bilayer buoyant dosage form.
5,169,638	Buoyant controlled-release powder formulation.
4,814,179	Floating sustained-release therapeutic compositions.
4,767,627	Drug delivery device that can be retained in the stomach for a controlled period of time.
4,167,558	Novel sustained-release formulations.
4,140,755	Sustained-release tablet formulations.
4,126,672	Sustained-release pharmaceutical capsules.
0013876 A1	Novel floating dosage form.

Figure 1. Anatomy of stomach

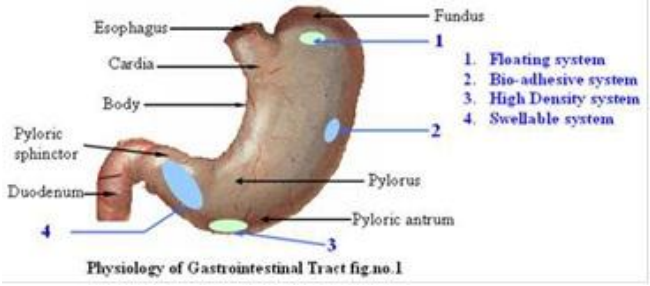

Figure 2. GI motility patterns

Figure 3. Volatile liquid containing system

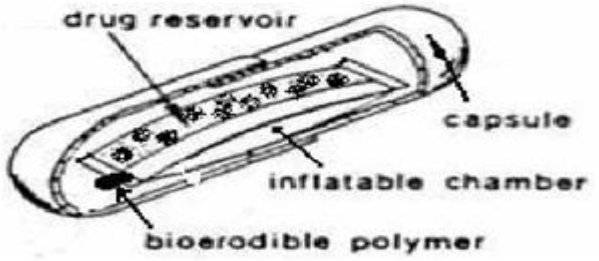

Figure 4. Gas generating system

Zhang J *et al.*, developed floating tablets of Captopril using HPMC K4M and K15M and Carbopol 934P. Study was summarized that buoyancy of tablet is by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the centre of the tablet [34].

Prepared and evaluated multiple-unit floating drug delivery system based on gas formation technique. In result the time to float dosage unit and coating level of gas-entrapped polymeric membrane decreased was decreased as amount of the effervescent agent increased. The drug release was sustained and linear with the square root of time. Drug release was decreased with Increasing coating level of gas-entrapped polymeric membrane. Both the rapid floating and the sustained release properties were achieved in the multiple-unit floating drug delivery system developed.

FUTURE PROSPECTS

Controlling the release of drug has been a major target for pharmaceutical research in past decades. This approach of floating can be used for various drug candidates and may controlled release dosage form get replaced by floating tablets with absorption phase of approximately 24 hr. But there are few issues which are still unsolved those are as below,

1) To determine efficiency of floating drug delivery system in fasted and fed state.
2) Use of buoyancy in enhancing GRT and FDDS and correlation between prolonged Gastric retention time and pharmacokinetic properties.

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