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Review Article

FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The aim of writing this review on gastro retentive and floating drug delivery system was to compile the new literature with the principle mechanism of floatation to acquired gastric retention. Various attempts have been made to develop gastroretentive delivery systems such as high density system, swelling, floating system. In floating multiple unit and single unit system are design and their classification and formulation aspect is cover in detail. These systems are very helpful to different problem solve during the formulation of different dosage form. In this review the gastric physiology and reported intra gastric delivery system have briefly been presented.

Keywords: floating drug delivery, hypochlorhydria, achlorhydria, mucoadhesive.

INTRODUCTION

The gastric emptying time and the variation in pH in different segments of gastrointestinal tract (GIT) are the major challenging task for the development of oral controlled release drug delivery system. Various attempts have been made to enhance the residence time of the dosage form within the stomach. Gastro retentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of the drug in the GIT. Potential drug candidates for gastro retentive drug delivery system (GRDDS) are drugs, which are locally active in the stomach eg. Misoprostol, antacids etc., and drugs that have narrow absorption window in GIT eg. L-DOPA, paraamino benzoic acid etc. In addition drugs which are unstable in the intestinal or colonic environment like captopril and metronidazole. It has been suggested that prolonged local availability of antimicrobial agents may augment their effectiveness in treating H. pylori related peptic ulcer. Moreover, it has been reported that bactericidal effect of clarithromycin and garcinol are time and concentration dependent. GRDDS however, are not suitable for drugs that may cause gastric lesions eg. Non-steroidal anti-inflammatory drugs. Also the drug substances that are

unstable in the strong acidic environment of the stomach are not the suitable candidates to be incorporated in such systems. In addition these systems do not offer significant advantage over the conventional dosage forms for drugs, which are absorbed throughout the GIT.

However, it is recognized that there are many physiological constraints, which may limit development of such delivery system.[1-10]

PHYSIOLOGICAL CONSIDERATIONS

Factors such as pH, enzymes, nature and volume of secretions, residence time, and effective absorbing surface area of the site of delivery play an important role in drug liberation and absorption.

The gastric pH is an important factor, which affects the performance of orally, administered drug. The gastric pH is not constant rather it is influenced by various factors like diet, disease, presence of gases, fatty acids and other fermentation products. Radio telemetry has been successfully used to measure the gastrointestinal pH in humans. The reported mean value of gastric pH in fasted healthy subjects is 1.1± 0.15, and the mean gastric pH in fed state in healthy males has been reported to be 3.6±0.4. This pH returns to the basal level in about 2 to 4 hours. Age, pathological conditions and drugs may influence gastric pH. About 20% of the elderly people exhibit either diminished (hypochlorhydria) or no gastric acid secretion (achlorhydria) leading to basal pH value over 5.0. Pathological conditions such as pernicious anaemia and AIDS may be significantly reduce gastric acid secretion leading to elevated gastric pH. The drugs like H_2 receptor antagonist and proton pump inhibitors significantly reduce gastric acid secretion. The mean pH value in fasted duodenum has been reported to be 5.8±0.3 in healthy subjects, and the fasted small intestine pH is reported to be 6.0±0.14.[11-15]

Normal gastric time usually ranges between 5 minutes to 2 hours. Depending on the fasted and fed state of the stomach, two distinct patterns of gastrointestinal motility and secretions have been observed. In fasted state the electrical activity of the stomach is governed by some cyclic contractile events commonly known as migrating myoelectric complexes (MMC). There are four consecutive phases of activity in the MMC.

Phase I – period of no contraction (30 to 60 minutes)

Phase II – period of intermittent contractions (20 – 40 minutes)

Phase III – period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave (10 to 20 minutes)

Phase IV – period of transition between phase III and phase I (0 to 5 minutes).

These cycles are disrupted by feeding, resulting in irregular contractile activity which may last for 3 to 4 hours. Thus frequent feeding may prolong gastric retention time.[16-21]

Another important factor that influences the gastric emptying is the caloric content of the meals. Fatty contents are emptied at slower rate than other contents. Acidity and osmolality also slows down the gastric emptying. Stress appears to cause an increase in gastric emptying rate, while depression slows it down. In general, women and elderly have a slower emptying rate than men and young people respectively. In addition, exercise, and body posture may influence the gastric emptying.

Apart from these physiological constraints there are certain other factors like density and size of the dosage form also influences the gastric emptying. Dosage forms having a density lower than that of gastric fluid experiences floating behavior and hence gastric retention. A density of <1.0 gm/cm^3 is required to exhibit floating property. Dosage forms having a diameter of more than 7.5 mm shows a better gastric residence time compared with one having 9.9 mm.[22-30]

APPROACHES TO PROLONG GASTRIC RESIDENCE TIME OF DRUG DELIVERY SYSTEM

Various devices such as mucoadhesive, swelling, high-density and floating systems have been developed to increase GRT of a dosage form. These delivery systems can be either in single (fluid filled floating chamber) or multiple (microspheres) unit system. Single unit formulations are associated with problems such as sticking and produce a serious problem of all or none release. Whereas multiple unit dosage forms are devoid of these disadvantages.

Floating System

The floating system is intended to float in and over the gastric contents resulting in prolonged GRT. Floating systems can be effervescent or non- effervescent in nature.

Effervescent System

Gas-generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.[31-35]

Ichikawa *et. al*[36] prepared a multiple unit floating pill, which consisted of a core seed surrounded by two different layers. The primary layer contained sodium bicarbonate and tartaric acid, which generated carbon dioxide in aqueous media. The outer layer composed of a swell able membrane that trapped the gas resulting in flotation of the system. The system started floating within 10 minutes of immersion into the test media and remained floated over a period of 5 hours.

Atyabi *et. al*[37] prepared coated ion exchange resin beads as gastro retentive delivery system. The resin had been charged with bicarbonate before it was coated with a semi permeable membrane of eudragit- RS. In the presence of hydrochloric acid bicarbonate was liberated, which formed carbon dioxide. The later was trapped inside the membrane resulting in flotation of the resin particle.

Uma maheshwari *et al*[38] developed a prolonged gastroretentive delivery system by combining both floating and bioadhesive techniques. They used ion exchange resins loaded with bicarbonate and acetohydroxamic acid; the particles were then coated with cellulose acetate butyrate by emulsion solvent evaporation method. The system exhibited floating ability due to the carbon dioxide generation when microgranules were exposed to gastric fluid. The mucoadhesiveness of the microparticles was examined by employing fluorescent probe.

Yang *et. al*[39] developed a swellable asymmetric triple layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in helicobacter pylori associated peptic ulcer using HPMC and poly ethylene oxide (PEO) as the rate controlling polymeric membrane excipient. The flotation was achieved by incorporating gas-generating layer consisting of sodium bicarbonate or calcium carbonate along with polymers. The in vivo results revealed that the sustained delivery of tetracycline and metronidazole over 6-8 hours could be achieved while the tablet remains afloat.

Volatile liquid containing systems

The GRT 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.[40]

Non Effervescent System

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to this dosage forms.

The most commonly used excipient in non effervescent floating drug delivery system are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polyacrylate, polymethacrylate and polycarbonate. After oral administration these dosage form swells in contact with gastric fluid and attains a bulk density of < 1 (Fig-1). The air entrapped within the swollen matrix imparts buoyancy to the dosage form.[41]

Colloidal gel barrier systems

Hydrodynamically balance system (HBS) was first design by Sheth and Tossounian[42] in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one

or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets

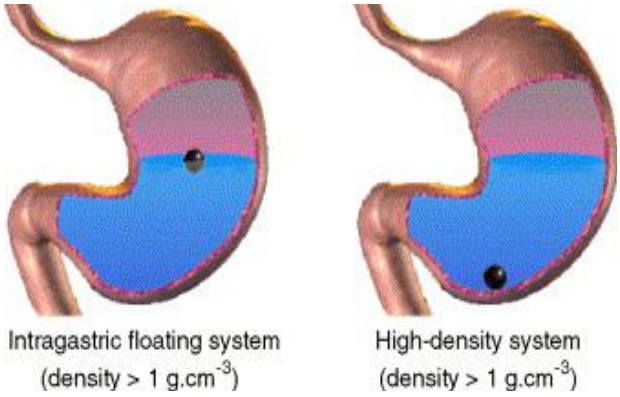

Fig. 1: Diagram of Gastroretentive drug delivery system (low density and high density systems)

or in capsules. 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.

Desai and Bolton[43] developed CR floating tablet of theophylline using agar and light mineral oil. Dispersing a drug/oil mixture in a warm agar gel solution made tablet and pouring resultant mixture into tablet molds, which on cooling and air drying forms floatable CR tablets.

Dennis *et. al*[44] described a buoyant CR powder formulation, which may be either filled into capsules or compressed into tablet. The formulation consisted of a drug, a pH dependent polymer, which was a water-soluble salt of alginic acid and a pH independent hydrocolloid gelling agent (such as HPMC, HPC etc.) and binder. The formulation was considered unique in a sense that it released the drug at a rate regardless of pH of the environment, being free of calcium ions and carbon dioxide producing material, and had drug release properties similar to a tablet of identical composition.

Microporous Compartment System

This technology is based on the encapsulation of drug reservoir inside a microporous 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. This technology was used by Harrigan[45].

Hollow Microspheres

Hollow microspheres are also known as microballoons. Hollow microspheres are prepared by emulsion solvent diffusion method. In this method a solution or dispersion of drug and polymer is prepared in solvent (like dichloromethane, ethanol, isopropanol or a combination of these). This dispersion/solution is introduced into an aqueous solution of PVA (polyvinyl alcohol) forming an O/W type emulsion. This emulsion is agitated using propeller type agitator to remove the organic solvent, which produces the microballoons, size between 500-1000 mm.

Kawashima *et. al*[31] prepared hollow microspheres with a drug loaded in their outer shells by an emulsion solvent diffusion method. The ethanol/dichloromethane solution of a drug and an enteric acrylic polymer was poured into an aqueous solution of PVA that was maintained at 40°C, with constant stirring. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with drug.

J.H. lee *et. al*[46] prepared floating acrylic resin microspheres with an internal hollow structure by solvent diffusion and evaporation method. Ethanol as a solvent in combination with isopropanol was used. The mechanism of formation of microsphere is reported, as ethanol a good solvent for acrylic polymer, preferentially diffuses out of dispersed droplets (organic phase) into an aqueous phase, the acrylic polymer instantly solidifies as a thin film at the interface between the aqueous phase and organic phase. It has also been reported that when the diffusion rate of solvent out of emulsion droplet was too slow, microspheres coalesced together. Conversely, when the diffusion rate of solvent was too fast, the solvent diffused into the aqueous phase before stable emulsion droplets could form, causing the aggregation of embryonic microsphere droplets.

Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, leading to the formation of porous system, which can maintain a floating force over 12 h.

Yong-Dan Tang *et. al*[47]prepared alginate beads based on the above method for the sustained release of both hydrophobic and hydrophilic drugs. They added sunflower oil in the beads and found the beads floating for 24 hours. The hydrophobic drug ibuprofen was released from this system for 24 hours due to oil partitioning.

Evaluation of floating dosage forms

Various parameters that need to be evaluated include floating duration, dissolution profiles, particle size analysis, flow properties, surface morphology, differential scanning calorimeter (DSC), incorporation efficiency, and micromeritic properties such as tapped density, true density etc. are also evaluated. Techniques such as γ scintigraphy, radiology, gastroscopy, ultrasonography, and MRI are also used for the evaluation.

The test for floating behaviour and drug release are generally performed in simulated gastric fluids 37°c[7].

Timmermans and Andre48 characterized the buoyancy capabilitiy of floating forms and sinking of non floating dosage forms using as apparatus to quantitatively measure the total floating force acting vertically on the immersed object. The apparatus operates by measuring continuously the force equivalent to F (as a function of time), which is required to maintain the submerged object. The object floats better if F is on the higher positive side.

F = f (buoyancy) – f (gravity)

F = (Db - Ds) gV

F – Total vertical force

Ds – Object density

Db – fluid density

V- Volume of fluid

g- Acceleration due to gravity

As reported by streubel *et. al*[49], a simple method for determining the floating behavior can be used. A definite no. of particles were placed into 0.1 N HCl, pH 1.2, containing 0.02% w/v tween 20(37°c) to exclude floating due to non wetted surfaces, followed by horizontal shaking. At predetermined time intervals, the flasks were allowed to stand for 5 minutes, without agitation and the no of settled particles was counted.

Surface morphology was observed by SEM and with the help of particle size analyzer; particle size distribution can be evaluated.

γ Scintigraphy[50]

Radiography[51]

Gastroscopy[52]

Ultra sonography[53]

MRI[54].

Table 1: Conventional v/s Gastroretentive drug delivery system

Conventional drug delivery system	**Conventional drug delivery system**
High risk of toxicity	Very low risk of toxicity
Less patient compliance	Improves patient compliance
Not suitable for delivery of drugs with narrow absorption window in Small intestine region	Suitable for delivery of drugs with narrow absorption window in small Intestine region.
Not much advantageous for	Very much advantageous for
Drugs having rapid absorption through GIT	Drugs acting locally in the stomach.
Drugs which degrade in the colon.	Drugs which degrade in the colon.
Drugs acting locally in the stomach.	Drugs having rapid absorption through GIT
Drugs which are poorly soluble at an alkaline pH	
No risk of dose dumping.	Possibility of dose dumping

EFFECT OF FORMULATION VARIABLES ON THE FLOATING PROPERTIES OF THE GASTRIC FLOATING DRUG DELIVERY SYSTEM

Shoufeng Li *et. al*[55] continuously monitored the floating kinetics of floating drug delivery system using a continuous

floating monitoring system which consisted of an electric balance interfacing with a computer. They studied the effect of several formulation variables, such as different types of HPMC, HPMC/Carbopol ratio, and addition of magnesium stearate. Addition of magnesium stearate significantly improved the floating capacity of GFDDS. HPMC of higher viscosity grades exhibited a greater floating capacity. For the polymer with same viscosity, i.e. K4M and E4M, the degree of substitution of functional group has not shown any significant contribution. A better floating behavior was observed at higher HPMC/Carbopol ratio. Carbopol appeared to have a negative effect on the floating behavior of the GFDDS.

Patel *et. al*[56] studied the effect of varying ratio of HPMC K4M to HPMC K100LV and SLS content on t50%, Q12, release rate constant and diffusion exponent. The release rate was higher at 1% SLS concentration compared to 2% SLS concentration and without SLS condition. This finding may be owing to the solubilization effect of SLS at 1% level, which is not observed at 2%, drug may have been entrapped in the micelle formation causing a decrease in rate of drug release.

Patel *et. al*[57] prepared floating tablets of carbamazepine by applying effervescent approach. Floating tablet of carbamazepine are prepared using polymers HPMC and ethyl cellulose. It was observed that as the amount of ethyl cellulose was increased in the formulation from 0% to 25%, the Flag decreased, whereas as the amount of HPMC K4M increased from 20% to 45%, the Flag increased, indicating that a high amount of HPMC K4M is undesirable to achieve low Flag.

Streubel *et. al*[49] studied the effect of type of polymer (PMMA, EC, and Eudragit) on the floating properties of microsphere. The release rate was maximum with eudragit RS, than ethyl cellulose and minimal with PMMA, which could be due to the different permeabilities of the drug with in these polymers. Eudragit RS and ethyl cellulose containing microparticle showed biphasic drug release; an initial burst effect followed by slower drug release phase. In contrast PMMA containing microparticles showed more sustained drug releases, which were not biphasic.

Narendra *et. al*[58] prepared bilayer floating tablets of Metoprolol tartarate. Effect of formulation variables on drug release and floating time was studied. When the total polymer content-to-drug ratio increased, the drug release rate at 8 hours decreased, whereas floating time increased. Floating time also increased by increasing HPMC: SCMC (sodium carboxy methyl cellulose) ratio. The polymer grade was found to have no effect on floating time.

Tang *et. al*[47] prepared floating alginate beads with calcium alginate, sunflower oil and drug. The alginate beads with oil addition were able to float over the medium for 24 hours under constant agitation, while non-oily beads could not. The buoyancy decreased for the beads with less oil inclusion or more drug incorporation. Thick coatings of eudragit also decreased buoyancy.

Sharma *et. al*[59] prepared a multiparticulate floating drug delivery system, using porous calcium silicate (fluorite RE) and sodium alginate. Meloxicam was adsorbed on the fluorite RE was used to prepare calcium alginate beads. An increase in FLR quantity in beads resulted in an increasing in floating lag time and decrease in sinking rate, probably because of the number of air trapped pores in beads increased with increase in FLR quantity.

Li *et. al*[1] developed a gastric system for oral controlled delivery of calcium. Three formulation variables, HPMC loading, citric acid loading and magnesium stearate loading were studied to know their effect on drug release and floating properties. All three-formulation variables significantly affected the drug release profile, whereas floating characteristic was affected by only HPMC loading.

POLYMERS IN FLOATING DRUG DELIVERY SYSTEM

Polymers play an important role in Controlled drug delivery system. As we know that FDDS is an approach to achieve drug release for long duration. Polymers, which can be successfully used in floating drug delivery system, are briefly discussed here. Acrylic polymers are widely used for the preparation of floating microspheres.

Lee *et. al* [46] has successfully used Eudragit S100 for the preparJain *et. al*[8] also reported the same findings about Eudragit. A good floating behavior was observed, whereas dissolution rate was found to be slow, because of the low solubility of eudragit at acidic pH. Kale et al[60] also reported the same findings.

LIST OF TABLE SHOWING VIEW OF DIFFERENT SCIENTIST BASED ON DIFFERENT POLYMER USED AND THEIR EFFECT IN FLOATING

Name of scientist	Polymer used	Floating effect
Lee *et. al*	Eudragit S100	The drug release rate and floating behavior both were reported good
Jain *et. al*	Eudragit	A good floating behavior was observed, whereas dissolution rate was found to be slow, because of the low solubility of eudragit at acidic pH
Kale *et. al*	Eudragit	A good floating behavior was observed, whereas dissolution rate was found to be slow, because of the low solubility of eudragit at acidic pH
Sungthongjeen *et. al*	Eudragit RL 30D, RS30D, and NE30D	The floating was reported for more than 24 hours.
Nepal *et. al*	Eudragit E100	The floating was reported for more than 24 hours
Tang *et. al*	Eudragit E100	The drug release rate and floating behavior both were reported good

Sungthongjeen *et. al*[61] prepared multiple unit floating drug delivery system based on gas formation technique. The pellets were consisting of an inner effervescent layer and an outer gas entrapping polymeric membrane of aqueous colloidal polymer dispersion of eudragit RL 30D, RS30D, and NE30D. Only the system, which uses eudragit RL30D, could float. The floating was reported for more than 24 hours.

Nepal et al[62] used eudragit E100 for the preparation of floating microspheres for fish farming. The findings were similar as reported earlier.

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