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New Concept: Floating Drug Delivery System

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach. An attempt has been made in this review article to introduce the readers to the current technological developments in floating drug delivery system.

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INTRODUCTION

Drug absorption from a gastrointestinal tract (GI) is a complex procedure and is subjected to many variables [1]. These variables make the *in-vitro* performance of the drug delivery systems uncertain [2]. The process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than the conventional dosage forms [3] such as, tablets, capsules, and granules. These physiological problems have been overcome by several drug delivery systems, by investigating the prolonged gastric retention time [4- 5]. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in the plasma drug concentration at a steady state by delivering the drug in a controlled and reproducible manner [6]. On the basis of the mechanism of mucoadhesion [7-8], flotation[9], sedimentation[10-11]or by the simultaneous administration of pharmacological agents[12-13] the controlled gastric retention of solid dosage forms may be achieved, which delay gastric emptying.

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In addition to this, a wide variety of both natural and synthetic hydrophilic polyionic systems such as alginates have been investigated for the preparation of multiple unit floating dosage forms.

In the present study, a multiple-unit FDF was designed keeping in view the 'all or nothing' response of single-unit systems[14]. Literature review indicates a widespread use of sodium alginate for achieving the sustained release of drugs[15-16] as it targets the gastric mucosa[17]and increase the bioavailability of the drugs[18] because of its ability to form a stable and bioadhesive gel with calcium ions[19]. Hydroxy propyl methyl cellulose (HPMC) has been reported to enhance the sustained release properties of alginate by providing a denser inner matrix[20]. Also the preparative methodology of alginate beads involves the use of aqueous solvents, avoiding exposure of the ingredients to high temperatures and toxic organic solvents[21-22] moreover, the resulting preparation is non-immunogenic, with bioadhesive properties that could serve as a potential advantage in stomach targeting.

Basic Gastrointestinal Tract Physiology

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum. The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is

the main site for mixing motions and act as a pump for gastric emptying by propelling actions[23]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours[24]. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[25].

- Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 4 to 6 minutes. 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 minutes 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 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

Factors Affecting Gastric Retention[26]

- **Density:** GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size:** Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.
- **Shape of dosage form:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes
- **Biological factors:** Diabetes and Crohn's disease.
- **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 every 1.5 to 2 hours. 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.
- **Nature of meal:** feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed:** the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age**: Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.
- **Single or multiple unit formulation:** Multiple unit formulations show a more Predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage for

Approaches to Design Floating Dosage Forms

Various approaches have been paused to increase the duration of oral dosage form in the

stomach, including floating systems, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices. (Magnetic systems, super porous –biodegradable hydro gel systems).

- Hydrodynamically balanced systems (HBS) – incorporated buoyant materials enable the device to float [27].
- Raft systems incorporate alginate gels – these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating [28].
- Swelling type of dosage form are such that after swelling, this product swell to extent that prevent their exit from the stomach through the pylorus. As, a result, the dosage form retained in the stomach for a longer period of time. These systems may be referred to as a "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters.
- High density formulations include coated pallets, and have density greater than that of the stomach content (1.004 gm/cm^3). This is accomplishing by coating the drug with a heavy inert material such as barium sulphate, ZnO, titanium dioxide. This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are position in the lower part of the antru[29].
- Another delayed gastric emptying approach of interest include sham feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decressing the gastric emptying rate and permitting considerable prolongation of the drug release.

Classification of Floating Drug Delivery Systems (FDDS)

Single Unit Floating Dosage Systems

Effervescent Systems (Gas-generating Systems)

These buoyant systems utilised matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach[30]. Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates[31] prepared floating bilayer tablets with controlled release for furosemide.

Non-effervescent Systems

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 these dosage forms. Examples of this type of FDDS include colloidal gel barrier microporous compartment system alginate beads[32],and hollow microspheres[33]. Another type is a Fluid- filled floating chamber[34] which includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behaviour. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates,passes off to the intestine, and is eliminated.

A newer Self-correcting floatable asymmetric configuration drug delivery system[35], has a 3-layermatrix to control the drug release. This 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the completion of

the release process. The system was designed in such a manner that it floated to prolong gastric residence time *in vivo*, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability.

Multiple Unit Floating Dosage Systems

In spite of extensive research and development in the area of HBS and other floating tablets, these systems suffer from an important drawback of high variability of gastrointestinal transit time, when orally administered, because of their all-or-nothing gastric emptying nature. In order to overcome the above problem, multiple unit floating systems were developed, which reduce the inter subject variability in absorption and lower the probability of dose-dumping. Reports have been found on the development of both non-effervescent and effervescent multiple unit systems.

Non-effervescent Systems

No much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported.

Effervescent Systems (Gas-generating Systems)

Ikura et al reported sustained release floating granules containing tetracycline hydrochloride. The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of HPMC, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. 60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule.

These minicapsules contain a central core and a coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the CO2 release in gastric fluid and the pepstatin resides in the stomach for prolonged period. Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic,biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues. A multiple unit system prepared by Iannuccelli *et al* comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads[36].

Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids[37-38], described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.

Evaluation of floating drug delivery systems

Various parameters need to be evaluated for their effects on gastric residence time of different formulations. These parameters can be categorized into the Following classes:

- Galenic: diametral size ('cut-off size'), resultant weight flexibility and density of matrices.
- Control: floating time, dissolution, specific gravity, content uniformity, and hardness and friability (of tablets).
- Geometric: shape
- Physiological: age, sex, posture, food and bioadhesion

Bio/mucoadhesive systems

Bioadhesive strength

Bioadhesive strength of a polymer can be determined by measuring the force required to separate a polymer specimen sandwiched between layers of either an artificial (e.g. cellophane) or a biological (e.g. rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an auto mated texture analyzer.

In-vivo evaluation

The effects of the mode of riboflavin-5-phosphate administration on the resulting mean drug plasma concentrations and cumulative amounts of riboflavin absorbed in dogs were studied. In contrast, with both a non-gastroretentive control formulation (multilayer film without rigid frame; 5.0 × 2.5 mm) and an oral solution, which resulted in shorter time periods with elevated riboflavin concentrations, the gastroretentive device (multilayer film with rigid frame; 5.0 × 2.5 mm) produced elevated plasma drug concentrations for at least 48 hrs. The absolute bioavailabilities were 17.1 ± 3.5%, 3.9 ± 0.4% and 3.9 ± 1% for the gastroretentive dosage form, control formulation and oral solution, respectively.

Magnetic systems

In-vitro dissolution study

In-vitro release experiments were carried out according to the US Pharmacopeia (USP) XXIII Paddle method at 37oC and 100 rpm, using 0.01 N HCl as dissolution medium. The measured values were continuously recorded using an IBM compatible AT computer (Friedrich, Munster, Germany). During the release experiments, the magnetic tablets were located at the wall of the release vessel 5 cm under the surface of the liquid, using an external magnet. The distance between the external magnet and the magnetic depot tablet was 8cm.The release from the tablet is directly proportional to the distance between the external magnet and tablet

In-vivo evaluation

Groning et al developed a method for determining the gastrointestinal transit of magnetic dosage forms of acyclovir under the influence of an extracorporeal magnet, using a pH tele-metering capsule (Heidelberg capsule). Small magnets were attached to the capsule and administered to humans. *In-vivo* human studies showed that, in the presence of an extracorporeal magnet, the plasma concentrations of aciclovir were significantly higher after 7, 8, 10 and 12 hrs. Furthermore, the mean area under the plasma concentration-time curve from zero to 24 hrs (AUC 0–24) was _2800 ng • h/mL with the external magnet and 1600 ng • h/mL without the external magnet.

Swelling and expanding systems

Water uptake study

The swelling of the polymers can be measured by their ability to absorb water and swell. Water uptake studies of the formulation (tablet or granules) are performed using USP dissolution apparatus II. The medium used is usually distilled water or 0.1 N HCl (900 mL) rotated at 50 rpm, and maintained at 37±0.5°C through-out the study. After a selected time interval, the formulation is withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets expressed in terms of water uptake (WU) are calculated as

WU (%) = Swollen weight – initial weight X 100/Initial weight

In-vitro dissolution studies in swelling and expanding systems are usually carried out by a modified dissolution method, as in the case of FDDS.

Floating drug delivery systems

In-vitro floating time determination

Floating time is determined by using the USP disintegration apparatus containing 900mL of 0.1 N HCl solution as a testing medium maintained at 37±0.5ºC. The time required to float different dosage forms is noted as floating (or buoyancy) lag time, and floating duration of the dosage form is determined by visual observation.

In-vitro dissolution study

Dissolution tests are performed using USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium; replenished with the same volume of fresh medium at sampling time points. Recent methodology as described in the USP XXIII states "the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of non-reactive material such as not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float". However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor

predictors of *in-vitro* performance for floating dosage forms.

Physiological parameters

Age, sex, posture, food, bioadhesion, health of subject and GIT condition[39].

Galenic parameter

Diametrical size, flexibility and density of matrices.

Control parameter

Floating time, specific gravity, dissolution, content uniformity, hardness and Friability.

Specific gravity

Specific Gravity of the floating system can be determined by the displacement method using benzene as a displacing medium[29].

Resultant weight

The *in-vitro* measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by fource equivalent to the fource F required to keep the object totally submerged in the fluid. This fource determines the resultant weight of the object when immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the fource and the resultant weight corresponds to the Victoria sum of buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the objects as shown in the equations:

$F = F_{buoy} - F_{grav}$
$F = dfgV - dfgV = (df-ds)\, gv$
$F = (df - M/V)\, gV$

In which the F is total vertical fource (resultant weight of the object), g is the Acceleration due to gravity, df is the fluid density, ds is the object density is the object mass and V is the volume of the object[40].

Applications of Floating Drug Delivery Systems

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained Drug Delivery

HBS systems 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 CR formulation hence can be overcome with these systems. These systems have a bulk density of G1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours) [41]. Similarly a comparative study [42],between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case.

Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets[43]. A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced[44].

Absorption Enhancement

Drugs that have poor bioavailability because of sitespecific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, 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 tablets (33.4%) and entericcoated LASIX-long product (29.5%).

CONCLUSION

The currently available polymer-mediated Noneffervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. Number of commercial products and patents issued in this field are the evidence of it. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. Some of the unresolved, critical issues like the quantitative efficiency of floating delivery systems in the fasted and fed states, role of buoyancy in enhancing GRT of FDDS and more than that formulation of an ideal dosage form to be given locally to eradicate H.Pylori, responsible for gastric ulcers world wide. With an increasing understanding of polymer behaviour and the role of the biological factors mentioned above, it is suggested that future research work in the FDDS should be aimed at discovering means to control accurately the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents. It seems that to formulate an efficient FDDS is sort of a challenge and the work will go on and on until an ideal approach with industrial applicability andfeasibility arrives.

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