The Pharma Research
Year: 2009, Vol: 01

Floating Controlled Drug Delivery Systems for Prolonged Gastric Retention: A Review

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ABSTRACT

Floating systems have the property of retaining the dosage units in the stomach for prolonged period of time and are useful for drugs acting locally in the gastro intestinal tract (GIT), drugs which are poorly soluble and unstable in intestinal fluids. Recently various efforts are being made to design floating systems such as Floating Drug delivery systems (FDDS), Swelling and Expanding Systems, Bioadhesive systems, Modified shape systems, High density systems etc. These systems are advantageous in improving GIT absorption of drug with controlled release due to specific site absorption limitations. The main objective of developing these systems is to increase the safety of a product to extend its duration of action and decrease side effects of drugs. These systems have more flexibility in dosage form design than conventional dosage form. Several approaches have recently been developed to extend gastrointestinal transit time by prolonging residence time of drug delivery system in the GIT.

Keywords: Floating drug delivery systems, Gastric retention, Bioadhesive systems, Modified shape systems, single units, and multiple units.

1. INTRODUCTION

Gastric emptying of dosage forms is an extremely variable 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 conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability.

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One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste,

and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.

GASTROINTESTINAL PHYSIOLOGY, PROBLEMS AND DESIGNING OF GASTRO RETENTIVE DOSAGE FORMS

The complex anatomy and physiology, variation in acidity, bile salts, enzyme content and mucosal absorptive surface of GI tract, from mouth to the rectum significantly influence the drug release, dissolution and absorption from orally administered dosage forms. Ritchel and Kearnsn (1999), Gupta and Robinson (1992), enlisted the various anatomical and physiological features of GIT.

There are two distinct modes of GI motility and secretary patterns in humans and animals, in fasted and fed state. As a result, the bioavailability of the orally administered drugs may be different depending on the state of feeding. Fasted state is associated with various cyclic events regulating the GI mobility patterns, commonly called as the migrating motor complex (MMC). The MMC is organizes into alternative cycles of activity and quiescence and can be subdivided into basal, pre burst and burst intervals also named as phase I, II and III, respectively.

Phase I: The quiescent period lasts for 30-60 minutes and is characterized by lack of any secretary and electrical activity and contractile motions.

Phase II: Exhibits intermittent action potential for 20-40 minutes with increasing contractile motions.

Phase III: Shows the prevalence of intense large and regular contractions that sweep off the undigested food. These are also called as "house keeper waves" and propagate for 10-20 minutes.

Phase IV: Is the transition period of 0-5 minutes between phase III and phase I.

These inter digestive series of electrical events originate in the foregut and propagates to terminal ileum in the fasted state and repeat cylindrically every system is administered in the fasted state, MMC may be in any of its phases and this can influence the total gastric residence time (GRT) and transit time in the GI tract. This assumes even more significance for drugs having absorption window, as this will affect the time the dosage form spends in the region preceding and around the window, the lesser the time spent, lesser would be the degree of absorption.

The Designing of a GRDF`s therefore should take into consideration following factors:

(i) In fasted state: resist gastric emptying during phase III of MMC.
(ii) In fed state: resist continuous gastric emptying through the pyloric sphincter.

This requires that the GRDF`s should become functional quickly after administration and be able to resist onslaughts of physiological events, for the desired period.

Factors Affecting Efficacy of GRDF`S
Various attempts have been made to retain the dosage forms in the stomach as a way of increasing the retention time. The various factors which influence the efficacy of GRDF`s as a gastro-retentive systems are:

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 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

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% to100% retention at 24 hours compared with other shapes.

Single and multiple unit formulations: 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 forms.

Fed or unfed state: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5 to 2 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 acids 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 of meal: 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 be increased 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 counter parts (4.6 ± 1.2 hours) regardless of the weight, height and body surface.

Age: Elderly people, especially those above 70, have a significantly longer GRT.

Posture: GRT can vary between supine and upright ambulatory states of the patient.

Concomitant drug administration: Drugs that are gastric emptying include poorly soluble antacids (aluminium hydroxide), anticholinergics (atropine, propantheline), narcotic analgesics (morphine) and tricyclic anti depressants (imipramine, amitriptyline). Metoclopramide, domperidone and cisapride (antiemetics) stimulate gastric emptying.

Biological factors: Diseases like gastroenteritis, gastric ulcer, pyloric stenosis,

diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hypothyroidism promote gastric emptying rate.

Approaches to Design Floating Dosage Forms:

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

Single-Unit Dosage Forms

In Low-density approach the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

Fluid- filled floating chamber type of dosage forms 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 behavior. 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. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/ml and is ~0.1 mg/ml at neutral pH).

HBS of chlordiazeopoxide hydrochloride had comparable blood level time profile as of three 10 mg commercial capsules. HBS can either be formulated as a floating tablet or capsule. Many polymers and polymer combinations with wet granulation as a manufacturing technique have been explored to yield floatable tablets.

Various types of tablets (bilayered and matrix) have been shown to have floatable characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropyl methylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose. Self-correcting floatable asymmetric configuration drug delivery system employs a

disproportionate 3-layer matrix technology to control drug release.

The 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. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation.

Multiple-Unit Dosage Forms:

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges, also referred to as "microballoons," have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In Carbon dioxide–generating multiple-unit oral formulations[28] several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.

Classification of Floating Drug Delivery Systems (FDDS)

The Floating drug delivery system (FDDS) can be divided into effervescent and non-effervescent systems.

(A) Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.

i. Volatile liquid containing systems:

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

ii. Gas generating systems:

These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the system,

thus decreasing its specific gravity and making it float over chime. A multiple unit type of floating pills, which generate CO_2, have also been developed. The system consists of a sustained release (SR) pill as seed, surrounded by double layers.

The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swellable membrane layer containing PVA, shellac etc. Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus, carbon-dioxide is released, causing the beads to float in the stomach.

(B) Non-effervescent systems

i. Colloidal gel barrier systems

Hydrodynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheth and Tossounian in 1975. These systems incorporate a high level (20-75%w/w) of one or more gel forming, highly swellable, cellulose type hydro-colloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

A bilayer tablet can also be prepared to contain are immediate release and other sustained release (SR) layer. Immediate release layer delivers the initial dose, whereas SR layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in a system with bulk density lesser than that of gastric fluid, and allows it to remain in the stomach for an extended period of time. A multilayer flexible, sheath like device buoyant in gastric juice showing SR characteristics have also been developed.

ii. Microporous compartment systems:

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. 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. Intragastric floating and SR granules of cellulose and calcium silicate as floating carriers, which had a characteristically porous structure with numerous pores and a large individual pore volume.

iii. Alginate beads:

Multiunit floating dosage forms have been developed from freeze dried calcium alginate. Spherical beads of approximate 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium chloride. After the interval gelation was complete, beads were separated from the solution and snap-frozen in liquid nitrogen before being freeze dried at -40^0C for 24 hours.

The results of resultant weight measurements suggested that these beads maintained a positive floating force for over 12 hours. Floating systems comprising of a calcium alginate core separated by an air compartment

from a membrane of calcium alginate or calcium alginate/polyvinyl alcohol (PVA) have also been developed.

There are several commercial products available based on the research activity of floating drug delivery (**Table 1**).

Table 1. Commercially available preparations

S. No.	Product	Active Ingredient
1	Madopar	Levodopa and benserzide
2	Valrelease	Diazepam
3	Topalkan	Alu. Mag. antacid
4	Almagate flatcoat	Antacid
5	Liquid gavison	Alginic acid and sodium bicarbonate

Formulation Development

To design and optimize oral controlled release formulations, the important step is to understand GIT dynamics such as gastric emptying, small intestine transit, colonic transit, etc. Now a sday's gamma-scintigraphy is used to understand the various physiological and pharmaceutical factors involved in oral drug delivery. Intelsite™® capsule is one of the most reliable and novel approach, which provides quick assessment of the oral absorption of drugs within specific regions of GIT.

The task of formulating a dosage form to achieve a desirable controlled residence in the stomach begins with selection of potential excipients that allow the formulation of matrices having controlled delivery characteristics, specific gravity less than that of gastric contents and it should dissolve slowly enough to serve as a reservoir for the delivery.

Evaluation of floating drug delivery systems:

The important parameters to be evaluated for their effects on gastric residence time of buoyant formulations can be mainly classified into following classes:

Galvanic parameters like size, flexibility, and density of matrices.

Controlled parameters like floating time, dissolution, specific gravity, content uniformity, hardness and friability (if tablets)

Geometric parameters like shape.

Physiological parameters like age, sex, posture, food and bioadhesion.

The test for buoyancy and Invitro drug release studies are generally carried out in simulated gastric and intestinal fluids maintains at 37°C. In practice floating time is determined by using USP XXII Disintegration apparatus containing 900 ml of 0.1 N HCl as a testing medium maintains at 37°C. In additional studies a modified standard dissolution vessel for more reliable assessment of the performance of floating dosage form is used.

The specific gravity of the floating dosage form can be determined by the displacement method using dosage form is usually determined by Roentgenography.

Future Potential

Floating dosage forms offer various future potential as evident from several recent

publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability. Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

The floating concept can also be utilized in the development of various anti-reflux formulations. It is also used to explore the eradication of Helicobacter pylori by using the narrow spectrum antibiotics.

Limitations:

The major disadvantages of floating systems are requirement of a sufficiently high level of fluids in the stomach for the drug delivery. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach. The dosage form should be administered with a minimum glass full of water (200-250 ml).

Floating system is not feasible for those drugs that have solubility or stability problems in gastric fluids. The drugs which are absorbed throughout gastro intestinal tract, which undergo significant first pass metabolism, are not desirable candidate. Some drugs present in the floating system causes irritation to gastric mucosa.

Conclusion:

In this review an attempt is made to summarize controlled/sustained release drug delivery with prolonged gastric residence time. Various gastric retention systems are useful for drugs with slow and incomplete intestinal absorption and drugs that have local effect in the stomach. The research in this area is ongoing and it will not be long before an improved system is developed.

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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Source of support: Nil, Conflict of interest: None Declared