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Review article

Floating drug delivery system: an updated review

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ABSTRACT

Recent technological and scientific research has been devoted to the development of rate controlled drug delivery systems to overcome physiological adversities such as short gastric residence times and unpredictable gastric emptying times. The floating or hydro-dynamically controlled drug delivery systems are useful in such application. The present review addresses briefly about the floating drug delivery systems. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

Keywords: Floating drug delivery bioequivalence, *In-vitro*, *In-vivo*.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control 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. 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[1]. Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices

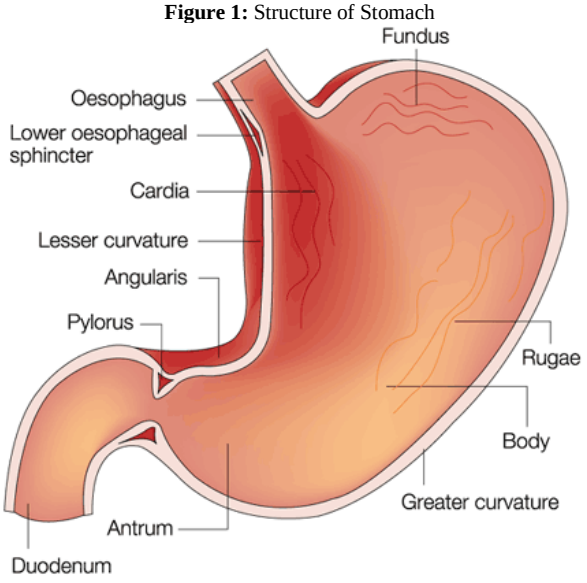
The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely[4]

The physiochemical characteristics of the drug

Anatomy and physiology of GIT.

Characteristics of Dosage forms

Figure 1: Structure of Stomach



Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To overcome this physiological problem, several

drug delivery systems with prolonged gastric retention time have been investigated. 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 plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner that are less soluble in high pH environment[2].

Floating drug delivery system

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres [1].

Basic gastrointestinal tract physiology

The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Substantial enzymatic digestion is initiated in stomach, particularly of proteins. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing.

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). 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.

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 interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.14 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 [2].

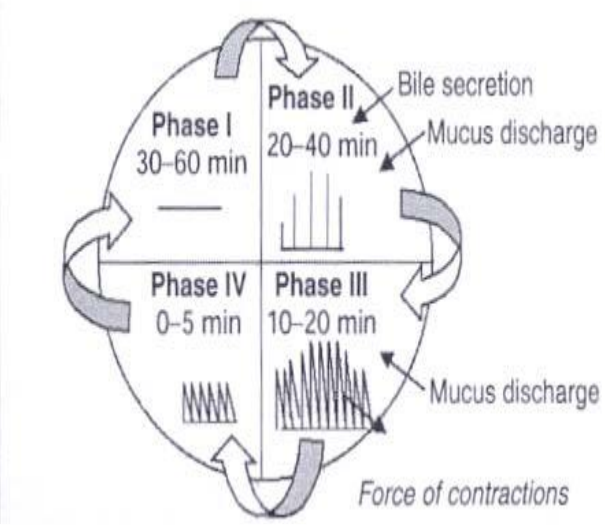
Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

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.

Figure 2: Motility pattern in GIure



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 [3].

Classification of floating drug delivery system

Single Unit Floating Dosage Systems

Non-effervescent Systems (Hydro dynamically balanced systems)

Effervescent Systems (Gas-generating Systems)

Multiple Unit Floating Dosage Systems

Non-effervescent Systems ((Hydro dynamically balanced systems)

Effervescent Systems (Gas-generating Systems)

Hollow Microspheres

Raft Forming Systems

Single Unit Floating Dosage System

Non-effervescent Systems (Hydro dynamically balanced systems)

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most commonly used excipient; although ethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethyl agar, carrageen or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining

surface hydration and buoyancy. Incorporation of fatty excipients gives low-density formulations and reduced penetration of water, reducing the erosion. Effective drug delivery depends on the balance of drug loading and the effect of polymer on its release profile.

Gas-generating systems

Floatability can also be achieved by generation of gas bubbles. Carbon dioxide (co_2) can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid, either the natural gastric acid or co-formulated as citric or tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.Gastric floating drug delivery system (GFDDS) offers numerous advantages over other gastric retention systems. These systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at desired rate from the stomach [4].

Multi –Unit Dosage Forms

The purpose for designing multiple-unit dosage form is to develop a formulation which has all the advantages of a single-unit form and also devoid the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed31. Microspheres with high loading capacity can be formulated using various polymers such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges, are referred as "microballoons," have been prepared32. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In Carbon dioxide–generating multiple-unit oral formulations 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.

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 CO2 to make the system less dense and float on the gastric fluids an antacid raft forming floating system.

Approaches to gastroretention

Several techniques are reported in the literature to increase the gastric retention of drugs [5].

High density systems: These systems, which have a density of ~3g/cm3, are retained in the rugae of stomach and capable of withstanding its peristaltic movements18, 20. The only major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8g/cm3. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high-density formulation

Swelling and expanding systems: These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells.

Mucoadhesive & bioadhesive systems: Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a sitespecific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.

Floating systems: Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.

Modified systems: Systems with non-disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device.

Advantages

Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine[6].

The gastroretentive system are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, and antacids [6].

Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.

The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.

FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids.

Treatment of gastrointestinal disorders such as gastroesophagealreflux.

Ease of administration and better patient compliance[2].

Site-specific drug delivery [7].

Disadvantages

Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.

Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.

These systems also require the presence of food to delay their gastric emptying.

Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

Drugs that cause irritation and lesion to gastric mucosa are not suitable to b e formulated as floating drug delivery systems.

Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Factors affecting gastric retention

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 9.5mm are reported to have an increased GRT

Shape of dosage form – The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened *in vivo* for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr12.

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 [8].

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Age – Elderly people, especially those over 70, have a significantly longer GRT.

Evaluation technique

Tablet Dimensions

Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

Weight Variation Test

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed show in table

Tablet Density

Tablet density was an important parameter for floating tablets. The tablet would floats only when its density was less than that of gastric fluid (1.004). The density was determined using following relationship.

$V = r^2h$ $d = m/v$

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (g/cc)

m = mass of tablet

Friability test

The friability of tablets was determined by using Roche Friabilator. It was expressed in percentage (%). Ten tablets were initially weighed (W) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_o). The % friability was then calculated by –

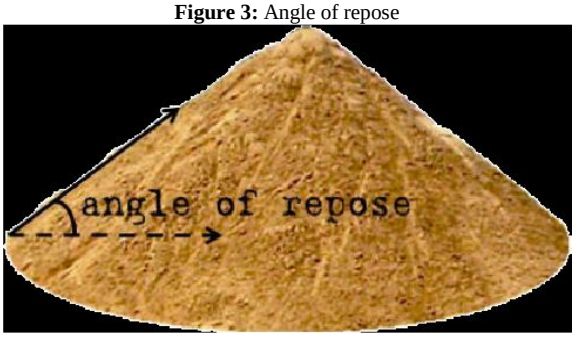
$$\%F = 100\ (1\text{-}W_0/W)$$

% Friability of tablets less than 1% was considered acceptable[8].

Angle of Repose

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Figure 3: Angle of repose



tan = h/r

θ**= tan-1 (h/r)**

θ = angle of repose

h = height of the heap

r = radius of the heap

The relationship between Angle of repose and powder flow is as follows in table

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Compressibility Index

The flow ability of powder can be evaluated by comparing the bulk density (ρo) and tapped density (ρt) of powder and the rate at which it packed down. Compressibility index was calculated by –

Compressibility index **(%) = ρt – ρo x 100**

ρt

Where **ρo =** Bulk density g/ml, **ρt** = Tapped density g/ml.

Application of fdds

Enhanced Bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

Sustained Drug Delivery

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.

Minimized Adverse Activity at the Colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.

Reduced Fluctuations of Drug Concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index [9].

CONCLUSION

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. Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. FDDS promises to be a potential approach for gastric retention. This article gives an overview of parameters affecting gastric emptying in humans as well as on the main concepts used to design pharmaceutical dosages form with prolonged gastric retention time.

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