FLOATING DRUG DELIVERY SYSTEMS - CHALLENGES & APPROACHES

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Abstract

The latest technical and scientific breakthroughs have ordained the creation of rate-controlled drug delivery systems. Gastro-retentive drug delivery systems have the potential to be used as controlled release drug delivery systems. Floating drug delivery system (FDDS) has sufficient buoyancy to keep the dose form in the gastric area for several hours, which is one of the different techniques to increase the Gastric Residence Time. Designing the Floating drug delivery system to maintain stomach retention aids in enhancing the drug's bioavailability and solubility as well as overcoming physiological challenges such as innumerable gastric emptying timings and gastric residency time. Drugs that are locally active and have a restricted therapeutic absorption window in the stomach or upper small intestine, are unstable in the intestinal or colonic environment, and have low solubility are of particular relevance to FDDS. The pharmaceutical basis for their design, classification, benefits, in vitro and in vivo evaluation parameters, and future prospects of FDDS have all been examined in length. The current review examines the floating drug delivery system's concept, mechanism, recent innovations, and applications.

Keywords: *Gastric Residence Time, Floating Drug Delivery Systems, Buoyancy, Therapeutic window.*

INTRODUCTION

The residence period of a traditional oral dose form is brief, and gastric emptying time is uncertain. The desire to localise medications in a specific region of the gastrointestinal tract (GIT), such as the stomach, led to the development of gastric retention. Because many medications are only absorbed in the upper GI tract, once-daily formulations are designed specifically for this route of administration.[1] As a result, gastrointestinal retention platforms arose. Drug delivery methods that gastroretentive are meant to stay in the stomach for an extended period of time. Gastroretentive drug delivery systems may be used as a controlled release medication delivery technique. One way for achieving prolonged gastric residence periods is to use a floating drug delivery system, which allows for both local and systemic drug action.[2]As a result, gastroretention may contribute to increased medication availability.

POTENTIAL MERITS OF FDDS

Floating dosage systems are drug delivery devices[3] that have a gastric retentive behaviour and provide a number of benefits. Here are a few examples:

Formulation process that is simple and traditional.

Drug delivery adapted to the location

Drugs are delivered in a controlled manner.

Drugs are delivered to a specific region in the stomach for long-term effect.

In the treatment of gastroesophageal reflux disease (GERD).

Patient compliance is improved due to the ease of administration.[4]

Limitations of FDDS

FDDS must be taken after a meal, however medication absorption is affected by the digestive state.[5]

The tendency of a medicine to float in the stomach is determined by how the individual is positioned.[6]

Drugs that have problems with solubility or stability in the stomach fluid are not good candidates for FDDS.

Certain medications, despite being easily absorbed in the stomach and undergoing effective first-pass metabolism, are not suited because slow gastric emptying can result in lower systemic bio-availability, such as nifedipine.[7]

The most significant disadvantage of a floating device is that it requires an adequate quantities of stomach fluids to remain without sinking. This constraint can be solved by covering the dose form with bio adhesive polymers that stick to the gastrointestinal mucosa easily.[8]

Drugs that are absorbed through the gastrointestinal tract and undergo first-pass metabolism are the most attractive options.

Certain medications in the floating system can irritate the mucosal linings of the stomach and cause discomfort.

Gastric emptying in floating systems can happen at any time and is greatly dependent on the parameters of the system. Drugs with a small absorption window in the GI tract (e.g. L-DOPA, para-aminobenzoic acid, Furosemide, riboflavin) Drugs that have a local effect in the stomach (e.g. Misroprostol, antacids) Intestinal or colonic drugs that are unstable (e.g. Captopril,

Ranitidine HCl, Metronidazole) Medications that disrupt the usual microbiota of the colon (e.g. antibiotics used for the eradication of Helicobacter pylori, such as Tetracycline, Clarithromycin, amoxicillin)
Drugs with low solubility at high pH levels (e.g. diazepam, chlordiazepoxide, verapamil) should not be taken before bedtime.

DRUG CANDIDATE APPROPRIATE FOR FDDS

Drugs have a specific absorption window in the GI tract.
Ex., L-DOPA, Aminobenzoic acid, Furosemide, and Riboflavin
Drugs that have a local effect in the stomach.[9]
Ex., Misoprostol, Antacids
Intestinal or colonic drugs that are unstable.
Ex. Captopril, Ranitidine HCl, Metronidazole
Drugs that disrupt the usual microflora of the colon.[10]
Ex. Antibiotics used for the eradication of Helicobacter pylori, such as Tetracycline, Clarithromycin, Amoxicillin
Drugs that have a limited solubility at high pH levels.[11]
Ex. Diazepam, Chlordiazepoxide, Verapamil

Stomach Physiology

The stomach is a component of the digestive system[12] that connects the oesophagus to the small intestine. Lymph nodes surround the stomach.

Stomach is divided into 5 regions

The first section of the stomach below the oesophagus is called the cardia. It houses the cardiac sphincter, a small muscular ring that helps prevent stomach contents from refluxing into the oesophagus.[13]
The circular area to the left of the cardia and below the diaphragm is known as the fundus.
The body is the stomach's largest and most important portion. This is where the food is combined and begins to decompose.[14]
The antrum is the stomach's lowest portion. The broken-down food material is held in the antrum until it is ready to be released into the small intestine. The pyloric antrum is another name for it.[15]
The region of the stomach that links to the small intestine is known as the pylorus. The pyloric sphincter, a thick ring of muscle that works as a valve to control the evacuation of stomach contents (chyme) into the duodenum, is located in this region (first part of the small intestine). The pyloric sphincter also prevents the duodenum's contents from returning to the stomach.[16]

Layers of the stomach wall

There are various layers of tissue in the stomach:
The mucosa (mucous membrane) is the stomach's inner lining. The mucosa has a ridged look when the stomach is empty. As the stomach fills up with foodstuff, these ridges (rugae) level out.

The mucosa is covered by the submucosa. It is made up of connective tissue, which includes larger blood and lymph vessels, nerve cells, and fibres.[17]
The next layer that covers the submucosa is the muscularis propria (or muscularis externa). It is made up of three layers of muscle and is the stomach's primary muscle.
The fibrous membrane that covers the outside of the stomach is known as the serosa. The stomach serosa is also known as the visceral peritoneum.[18]

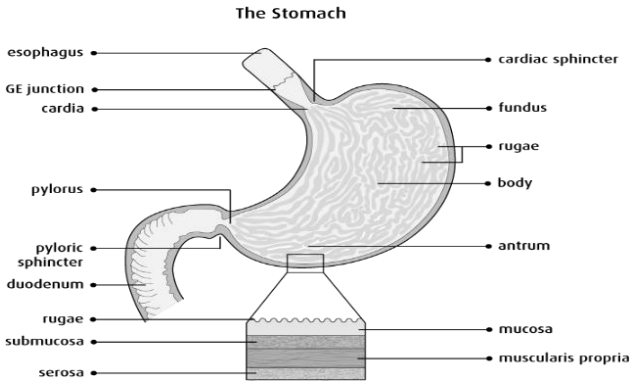

Figure: 1. Physiology of Stomach

Gastrointestinal Motility

The fasting and fed states have two different patterns of gastrointestinal motility and secretion. As a result, depending on the stage of eating, the bioavailability of orally delivered medications will vary.[19] It is characterised by an inter-digestive series of electrical events and cycles every 2–3 hours in the fasted state, both through the stomach and small intestine. The interdigestive myoelectric cycle, or Migrating motor complex, is the name given to this action (MMC). MMC intervals are commonly split into four phases: basal (Phase I), pre-burst (Phase II), burst (Phase III), and phase IV.

Phase I (Base Phase) lasts 40–60 minutes and has only a few contractions.

Phase II (Pre-Burst Phase) lasts 40–60 minutes and is characterised by intermittent action potential and contractions. The strength and frequency of the attacks gradually increase as the phase advances.[20]

Phase III (Burst Phase) lasts 4–6 minutes. It consists of short bursts of powerful and regular contractions. The undigested material is swept out of the stomach and into the small intestine as a result of this spasm. The housekeeping wave is another name for this.[21]

Phase IV lasts 0–5 minutes and happens twice in a row between phases III and I.
The fed state's motor activity begins 5–10 minutes after a meal is consumed and lasts as long as food is present in the stomach. The longer the period of fed activity, the more food ingested, with normal time spans of 2–6 h, and more commonly 3–4 h, with phasic contractions comparable to MM Gastrointestinal motility Phase II.

APPROACHES TO FDDS

A. NON-EFFERVESCENT SYSTEMS

After ingesting, this sort of system expands due to gastric fluid inhibition, preventing them from exiting the stomach.[23] The medicine is mixed with a gel, which swells when it comes into touch with the stomach fluid while maintaining relative shape integrity and a bulk density of less than one within the outer gelatinous barrier.[24] The air contained by the expanded polymer gives these dose forms buoyancy. HPMC, polyacrylate polymers, polyvinyl acetate, carbopol agar, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates are among the most often utilised excipients in these systems. This system can be further broken down into four types:

Colloidal Gel Barrier System

These systems contain drugs that have gel-forming hydrocolloids in them, allowing them to float in the stomach contents. This prolongs GRT and increases the amount of medication at the absorption site in solution form, allowing for faster absorption. One or more gel-forming, highly soluble cellulose type hydrocolloids, such as hydroxypropyl cellulose and hydroxyethyl cellulose, are used in this method.[25] When this hydrocolloid comes into touch with gastric juice, it hydrates and creates a colloid gel barrier around its surface, which aids in the drug's sustained release.[26]

Microporous Compartment System

A drug reservoir is contained inside a microporous compartment having pores on the top and bottom walls in this technology. The drug reservoir compartment's peripheral walls are entirely sealed. This shield prevents the undissolved medication from coming into direct touch with the stomach surface. The delivery system's flotation chamber floats above the stomach content that has become imprisoned in air. Gastric fluid enters through an opening, dissolves the drug, and transports the dissolved drug all over the intestine for absorption on a continuous basis.[27]

Alginate Beads

The freeze dried calcium alginate was utilised to create multi-unit floating dosage forms. [28] Calcium alginate can be precipitated by dropping sodium alginate solution into aqueous calcium chloride solution to make spherical beads with a diameter of around 2.5 mm. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40oC for 24 hours, resulting in a porous system with a floating force of more than 12 hours. The residence time of these floating beads is more than 5.5 hours.

Hollow Microspheres/Microballons

An ethanol/ dichloromethane solution containing the drug and an enteric acrylic polymer were injected into an agitated solution of poly vinyl alcohol (PVA) that was thermally regulated at 40oC to generate hollow microspheres loaded with drug in their outer polymer shell.[29] The evaporation of dichloromethane created in the internal cavity of the polymer and drug microsphere generates the gaseous phase in the scattered polymer droplet. For more than 12 hours, the micro balloon floated continuously over the surface of an acidic dissolving fluid containing surfactant.[30]

B. EFFERVESCENT SYSTEMS

Swellable polymers such as methocel polysaccharides (e.g., chitosan) and effervescent components are used in these buoyant systems (e.g., sodium bicarbonate, citric acid or tartaric acid). When it reaches the stomach, the system is so well prepared that carbon dioxide is released, causing the formulation to float.[31]

Super Porous Hydrogel

Despite the fact that these are swellable systems, they are distinct enough from the standard types to justify their own classification. Water absorption by traditional hydrogels is a sluggish process with pore sizes ranging from 10 nm to 10 m, and it may take many hours to reach an equilibrium condition during which premature evacuation of the dosage form may occur. Due to rapid water uptake by capillary wetting through numerous interconnected open pores, super porous hydro gels with an average pore size of > 100 m swell to equilibrium in less than a minute. Furthermore, they swell to a large size and are designed to endure the pressure exerted by gastric contractions.[32]

Magnetic Systems

The magnetic dosage forms have a tiny magnet and an extra-corporal magnet that regulates the dosage form's gastrointestinal transit. Despite the fact that these devices appear to operate, the external magnet must be placed with extreme precision, which may affect patient compliance.[33]

Floating Drug Delivery System

Floating systems, initially reported by Davis in 1968, are low-density systems with enough buoyancy to float over gastric contents and stay in the stomach for an extended period of time. The drug is gently released at the desired pace while the system floats over the gastric contents, resulting in greater GRT and less variation in plasma drug concentration.[34]

Swelling and Expandable Systems

The expandable GRDF are usually based on three configurations: a small ('collapsed') form that allows for easy oral intake; an expanded form that is attained in the stomach and thus inhibits passage through the pyloric sphincter; and finally, a small form that is obtained in the stomach when preservation is no longer required, i.e. after the GRDF has set to release its active ingredient, allowing for evacuation.[35]

Swelling or unfolding in the stomach might be used to create the desired enlargement. Osmosis is the most common cause of swelling. The GRDF is produced in an enormous diameter and folded inside a pharmaceutical carrier, such as a gelatin capsule, enabling easier intake due to mechanical shape memory.[36] The carrier dissolves in the stomach, and the GRDF spreads or extends out.

Raft Forming System

Antacid distribution and therapeutic delivery for gastrointestinal infections and illnesses have gotten a lot of interest thanks to raft forming systems. Gastric oesophageal reflux disease has been treated with floating rafts (GERD). The formation of a raft occurs when a viscous cohesive gel comes into touch with stomach fluids, causing each section of the liquid to inflate and create

an uninterrupted layer known as a raft. Because of the low bulk density caused by CO2 production, this raft floats on gastric contents.[37] To make the system less dense and float on the stomach fluids, it usually comprises a gel forming agent and alkaline bicarbonates or carbonates responsible for CO2 creation.

Gas Generating System

This is a buoyant delivery method made with effervescent substances such as sodium bicarbonate, tartaric acid, and citric acid, as well as a low density polymer. This device used an effervescent reaction when the medicine came into contact with the stomach juice, which caused the system to produce carbon dioxide gas, which caused the fluid to permeate into the tablet, causing the tablet to float.[38] The floating tablet concept is based on a matrix type drug delivery system in which the drug stays embedded in the matrix system and is dispensed without the tablet disintegrating. Effervescent floating tablets can be used as a long-acting dose form to avoid some of the drawbacks of traditional dosage forms.[39] This also improves drug bioavailability by reducing drug concentration variations.

Volatile Liquid Containing Systems

A drug delivery system's GRT can be maintained by including an expandable chamber containing a liquid, such as ether or cyclopentane, that gasifies at body temperature and causes the chamber to inflate in the stomach.[40] The device may additionally include a bio erodible plug composed of PVA, Polyethylene, or other biodegradable material that dissolves over time, enabling the expandable chamber to release gas and deflate after a specific time, allowing the tablet to be ejected spontaneously.

FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM

Size and Shape

When comparing dosage form units with a diameter of more than 7.5 mm to those with a diameter of 9.9 mm, it has been stated that those with a diameter of more than 7.5 mm have a higher GRT. When compared to other shapes, the dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilo-pond per square inch (KSI) have greater GIT retention for 90 to 100 percent retention at 24 hours.

Density

The dosage form's density should be less than the contents of the stomach (1.004gm/ml).

Nature of the Meal

Feeding indigestible polymers of fatty acid salts to the stomach can cause it to shift its motility pattern to a fed state, slowing gastric emptying and extending therapeutic release.[41]

Sustained Release Drug Delivery System

HBS systems can stay in the stomach for extended periods of time, allowing the medicine to be released over time.[42] Limited stomach residence time is a concern that can be overcome with these systems when using an oral CR formulation. Because these systems have a bulk density of 1, they can float on the contents of the stomach. Because these networks are

relatively large, going through the pyloric aperture is banned, for example. Nicardipine hydrochloride[43] floating capsules with a long release time were created and tested *in vivo.*

Site-specific drug delivery

These systems are especially useful for medications that must be absorbed from the stomach or the anterior section of the small intestine, such as riboflavin and furosemide. The stomach absorbs the most furosemide, followed by the duodenum. A monolithic floating dosage form with a longer stomach residence time was devised, and the bioavailability was enhanced, according to the study. The floating tablets produced an AUC that was almost 1.8 times that of regular Furosemide tablets.[44]

Absorption Enhancement

Drugs with low bioavailability due to site specific absorption from the upper gastrointestinal tract could be formulated as floating drug delivery systems, resulting in a significant increase in bioavailability (42.9 percent) when compared to commercially available LASIX tablets (33.4 percent) and enteric coated LASIX-long product (29.5 percent).

Using rabbits, the formulation was compared to commercially available MICARD capsules. When compared to standard MICARD capsules, the sustained release floating capsules had a longer administration time (16 hours) (8 hours).

Floating medication delivery has a number of applications for pharmaceuticals with low bioavailability due to the upper gastrointestinal tract's restricted absorption window. It keeps the dose form at the absorption site and so improves bioavailability.

EVALUATION PARAMETERS FOR FDDS

Particle Size Determination

In order to determine the particle size and size distribution of beads or microspheres in the dry condition, optical microscopy is performed.

Surface Characterization

The exterior and cross-sectional morphology (surface characterisation) are examined using scanning electron microscopy (SEM).

Weight Determination

Bulk density and floating duration have been the most commonly used metrics to assess the buoyancy of a dosage form. Although single density determination does not anticipate the dosage form's floating force evolution since the dry material used to make it gradually reacts or interacts with the gastric fluid to release the pharmaceutical contents, it does predict the dosage form's floating force evolution. The genuine floating abilities of the dose form as a function of time were calculated using a unique method. Bulk density and floating duration have been the most commonly used metrics to assess the buoyancy of a dosage form. Although single density determination does not anticipate the dosage form's floating force evolution since the dry material used to make it gradually reacts or interacts with the gastric fluid to release the pharmaceutical contents, it does predict the dosage form's floating force evolution.[45]

Swelling Index and water uptake (WU)

Water intake can be examined using the swelling behaviour of the Floating dose form. The study entails submerging the dosage form in simulated gastric fluid at 37°C and measuring changes in parameters such as tablet diameter and thickness at regular 1 h intervals until the tablets were removed from the beaker and the excess surface liquid was thoroughly wiped with paper. After reweighing the enlarged tablts, WU was determined using an equation to calculate percent weight gain.

$$WU = (Wt - Wo) \times 100 / Wo$$

The weights of the dosage form at time t and initially are Wt and Wo, respectively.

Floating Lag Time

Floating lag time is the amount of time it takes for a tablet to rise to the upper quarter of the dissolution vessel after being introduced into the medium.

Floating Time

The floating time or flotation time is the amount of time it takes for the dose form to float. These tests are usually carried out in simulated gastric fluid or 0.1 mole 3.lit1 HCl at 37°C utilising a USP dissolving device and 900 ml of 0.1molar HCl as the dissolution medium.[46]

***In -vitro* Drug Release Studies**

In-vitro drug release studies are frequently carried out in simulated stomach and intestinal fluids kept at 37^0 degrees Celsius. The tests were carried out using the USP dissolving device. Sink conditions are maintained by periodically withdrawing samples from the dissolution medium, replacing them with the same volume of fresh medium, and analysing them for drug content after an adequate dilution.[47] The dosage units that would ordinarily float can be attached to a small, non-reactive piece of non-reactive material, such as a few twists of wire helix. However, standard dissolution procedures based on the USP or the British Pharmacopoeia (BP) have been shown to be poor predictors of floating dosage form *in vitro* performance.

Drug Entrapment Efficiency

Gamma Scintigraphy

In in-vivo study, X-Ray/Gamma Scintigraphy is the most important evaluation criteria for floating dose forms. In each experiment, the animals are fasted overnight with free access to water, and a radiograph is performed shortly before the floating pill is given to ensure that no radioopaque material is present.

The presence of a radioopaque material allows the dose form to be visualised using X-rays. The formulation is administered by natural swallowing, followed by 50 mL of water.[48] Each animal's radiographic imaging is taken while it is standing, and the distance between the X-ray source and the animal should remain consistent throughout the imaging to allow for easy detection of tablet movement.

For a total of 5 hours, an Xray machine was used to perform stomach radiography at 30 minute intervals.

Gamma scintigraphy is a noninvasive in-vivo imaging technique that involves the use of a short-lived gamma emitting radioisotope to observe the transit of a dosage form to its intended delivery site. Observing an emitting Radionucleide in a formulation with a camera or a scintiscanner allows for indirect exterior observation. The main disadvantages of scintigraphy are the associated ionising radiation for the patient, the limited topographic information, low resolution inherent in the technology, and the tedious and expensive manufacture of radiopharmaceuticals.[49]

Pharmacokinetic Studies

AUC (Area under curve), C_{max}, and time to reach maximum plasma concentration (t_{max}) were all calculated using a computer in pharmacokinetic investigations.

FUTURE CHALLENGES OF FDDS

Antiviral, antifungal, and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, and tetracyclines) that are absorbed from very particular regions of the GI tract and whose advancement has been halted due to a lack of appropriate pharmaceutical technologies can all benefit from the FDDS approach. Furthermore, the dosage form may enable for more effective oral usage of peptide and protein medications such as calcitonin, erythropoetin, vasopressin, insulin, low molecular weight heparin, and LHRH by continuously providing the drug to its most efficient site of absorption.

The quantitative efficiency of floating delivery systems in the fasted and fed phases, as well as the association between prolonged GRT and SR/PK features, are some of the unresolved essential concerns related to the rational development of FDDS. However, we are as close as we've ever been to seeing a more rapid transfer of gastric retention devices from the research and development stage to manufacturing and commercialization.

SUMMARY AND CONCLUSION

Polymer-mediated non-effervescent and effervescent FDDS, based on delayed stomach emptying and buoyancy principles, promise to be a very successful technique of modulating controlled oral drug delivery. It is evidenced by the number of commercial goods and patents issued in this subject. For medications that are absorbed largely in the upper GI tract, such as the stomach, duodenum, and jejunum, the FDDS becomes an extra benefit. Some of the irresolvable, critical issues include the quantitative efficiency of floating delivery systems in fasted and fed states, the role of buoyancy in enhancing GRT of FDDS, and, more importantly, the formulation of a suitable dosage form to be given locally to eradicate H.Pylori, the bacteria that causes gastric ulcers around the world. With a better understanding of polymer behaviour and the role of the biological factors mentioned above, it is suggested that future research in the FDDS should focus on finding ways to precisely control the drug input rate into the GI tract in order to optimise the pharmacokinetic and toxicological profiles of medicinal agents. Forming an efficient FDDS appears to be a difficulty, and development will continue until an optimum technique with industrial usability and feasibility is found.

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