Int J Pharma Res Health Sci. 2018; 6 (5): 2755-62
DOI:10.21276/ijprhs.2018.05.01
Pattanayak *et al.*
CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Review Article

A Review on Floating Drug Delivery Systems in Present Scenario

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ARTICLE INFO

Received:19 Sep 2018
Accepted:20 Oct 2018

ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) is to compile the recent literature with special focus on the types of floating drug delivery systems, principal and mechanism of floatation to achieve gastric retention. Drug delivery systems are those that float immediately upon contact with gastric fluids present promising approaches for increasing the bioavailability of drugs with absorption windows in the upper small intestine. However, immediate floating can only be achieved if the density of the device is low at the very beginning. Devices with an initially high density (which decreases with time) first settle down in the stomach and, thus, undergo the risk of premature emptying. Inherent low density can, for example, be provided by the entrapment of air or by the incorporation of low density materials or foam powder. This review explains briefly about factors affecting floating system, evaluation parameters and application of the system.

Keywords: Gastric residence time, Floating Drug Delivery System, In-vitro evaluation

1. INTRODUCTION

The oral route represents nowadays the predominant and most preferable route for drug delivery.[1] Gastric emptying time and the variation in pH in different segments of GIT is the major challenging task for the development of controlled release drug delivery system.[2] Floating systems are low density system that float over the gastric contents and increased gastric retention time and a better control of the fluctuations in plasma drug concentration. That float immediately upon contact with gastric fluids present promising approaches for increasing the bioavailability of drugs with absorption windows in stomach or upper small intestine, unstable in the intestinal or colonic environment

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and exhibit low solubility at high ph values.[3] This is achieved by obtaining a zero-order release includes drug release from the dosage form that is independent of the amount of drug in the delivery system.[4]

Advantages of floating dosage form: [5]

1. Advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. eg. Riboflavin and Furosemide
2. Fluctuations in plasma drug concentration are minimized
3. Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine
4. Keeps the drug in floating condition in stomach to get relatively better response in certain conditions like diarrhoea.

Limitations of Floating Drug Delivery Systems:[5]

1. A high level of fluid in the stomach is required for drug delivery to float and work efficiently.
2. Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.
3. Drugs such as nifedipine, which under goes first pass Metabolism may not bedesirable for the preparation of these
4. Drugs which areirritant to Gastric mucosa are also not desirable.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

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.[6] 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. 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.[7]

- 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 occur 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.

2.FACTORS AFFECTING GASTRIC RES IDENCE TIME OF FDDS

a) Formulation factors

Size of tablets:

Retention of floating dosage forms in stomach depends on th e size of tablets. Small Tablets are emptied easily from the stomach as compared to larger tablets during the house keeping waves.[8] Floating and non-floating capsules of three different sizes having a diameter of 4.8mm, 7.5mm and 9mm were formulated and analysed for their different properties.[9]

Density of tablets:

Density is the main factor affecting the gastric residence tim e of dosage form.Floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities.[10]

Shape of tablets:

The shape of dosage form is one of the factors that affect its gastric
residence time. Six shapes (ring tetrahedron, cloverleaf, strin g, pellet, and disk) were screened in vivo for their gastric ret ention potential.[11]

Viscosity grade of polymer:

Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction.
Low viscosity polymers were found to be more beneficial than high viscosity polymers in improving floating property.[12]

b) Idiosyncratic factors

Gender;

Women have slower gastric emptying time than do men.[13]

Age: Low gastric emptying time is observed in elderly than do in younger subjects. Elderly
people, especially those over 70 years have a significantly lo nger GRT.[14]

Posture: An upright position protects floating against postprandial emptying. Supine position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms experience prolonged retention.[15,16]

Concomitant intake of drugs: Drugs such as prokinetic age nts (e.g., metoclopramide and
cisapride), anti Cholinergics (e.g., atropine or propantheline) , opiates (e.g., codeine) may affect the performance of FDDS. The co-administration of GI motility decreasing drugs can increase gastric emptying time[16]

Feeding regimen: Gastric residence time increases in the pr esence of food, leading to increased drug dissolution of the d osage form at the most favorable site of absorption.[17]

3. MECHANISM OF FLOATING SYSTEMS

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. 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. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. 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. To measure the floating force kinetics, a novel apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side.

$F = (Df - Ds)\, gv$ ……..(1)

Where, F= total vertical force,

Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity[18]

4. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

***Effervescent System FDDS*:** These are matrix type of system. Prepared with the help of swellablepolymers such as methylcellulose and Chitosan with various effervescent compounds. Ex: sodium bicarbonate, tartaric acid, citric acid. These are formulated in such a way that when they come in contact with gastric content, CO_2 is liberated and gets entrapped in swollen hydrocolloid which provides buoyancy to dosage form. The design of delivery system was based on swellable asymmetric triple layer tablet approach[19].

Gas Generating Systems: These are low density FDDS is based on the formation of CO_2 within the device following contact with body fluids. The materials are fabricated so that upon arrival in stomach, $CO_2$is liberated by acidity of the gastric content and is entrapped in the gellified hydrocolloid this produce upward motion of the dosage form and maintain its buoyancy. Decrease in specific gravity cause dosage form to float on the chyme .The CO_2generating components may be intimately mixed within the tablet matrix in which case a single layer or bilayer is produced which contain the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a sustained release effect[(20,21)].

***Volatile Liquid Containing Systems (Osmotically Controlled DDS)*:** As an osmotically controlled floating system, the device comprises of a hollow deformable unit that is convertible from a collapsed position after an extended period of time. A housing is attached to the deformable unit and it is internally divided into a first and second chamber with the chambers separated by an impermeable, pressure responsive movable bladder. The first chamber contains an active drug , while the second chamber contain a volatile liquid, such as cyclopentane or ether that vaporises at physiological temperature to produce a gas, enabling the drug reservoir to float. To enable the unit to exit from the stomach, the device contains a bio erodible plug that allowed the vapour to escape.[22]

***Non-Effervescent FDDS*:** Non-Effervescent FDDS use a gel forming (or) swell able cellulose type of hydrocolloids, Polysaccharide, matrix forming polymer like polycarbonate, polymethacrylate and polystyrene. One of the formulation methods involves the mixing of the drug with gel forming hydrocolloids which swell in contact with gastric fluid after oral administration and maintains integrity of shape and a bulk density barrier, the air trapped by swollen polymer confer buoyancy to the dosage forms. [23]

Colloidal Gel Barrier Systems (Hydrodynamic Balanced Systems): Such system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption site in the solution form for ready absorption, this system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid e.g.(HPMC),polysaccharides and matrix forming polymer such as polycarbophil, polystyrene and polyacrylate. On coming in the contact with GI fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface[24].

***Micro porous Compartment Systems*:** This technology is based on the encapsulation of a drug reservoir inside a Micro porous compartment with pores along its top and bottom walls. The peripheral wall of the drug reservoir compartment is completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the gastric fluid to an extent that it prevents their exist from the drug and carrier the dissolved drug for continuous transport across the intestine for absorption.[25]

Floating Microspheres / Micro balloons: Hollow microspheres are considers as most promising buoyant system as they are more advantageous because of central hollow. Hollow microspheres are loaded with drug and their

outer polymer shelf was prepared by a novel emulsion solvent Diffusion method. [26]

***Alginate Beads / Floating Beads*:** Multi-unit floating dosage forms have been developed from freeze calcium alginate[27]. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are than separated, snap-frozen in liquid nitrogen and freeze-dried at 400°C for 24 h, leading to the formation of a porous system, this can maintain a floating force for over 12 hr. These floating beads gave a prolonged residence time of more than 5.5 h.

***Raft forming systems*:** Raft forming systems have received much attention for the delivery of antacid and drug Delivery for gastro infection and disorders. On contact with gastric fluid the gel forming solution swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles. This Forms raft layer on top of gastric fluid which releases drug slowly in stomach. (Often used for gastro oesophageal reflux treatment).[28]

APPROACHES FOR INCREASING GASTRIC RETENTION TIME

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach.

***High-density systems*:** These systems, which have a density of ~3 g/cm3, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm3, such systems can be retained in the lower part of the stomach.[29,30]

***Swelling systems*:** After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time.

***Bio/mucoadhesive systems*:** Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the gastric residence time (GRT) by increasing the duration of contact between the dosage form and the biological membrane[32,33].

***Floating systems*:** Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period.[34]

***Incorporating delaying excipients*:** Another delayed gastric emptying approach of interest included feeding of digestible polymers of fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delayed release excipients like triethanolaminemyristate in a delivery system.[35]

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[36].

SUITABLE DRUGS FOR GASTRORETENTION:[5]

Delivery of the Drugs in continuous and controlled manner have a lower level of side effects and provide their effects without the need for repeated dosing or with a low dosage frequency.

1. Narrow absorption window in GI tract, e.g., riboflavin and levodopa Narangetal.
2. Basically absorbed from stomach and upper part of GIT, e.g. chlordiazepoxide and cinnarazine.
3. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
4. Locally active in the stomach, e.g., antacids and misoprostol.
5. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.

5. EXCIPIENTS USED IN FDDS [37,38,39]

***Polymers*:** Polymers are long chain organic molecules assembled from many smaller molecules called as monomers. It is used in the preparation of FDDSfor targeted to GIT.

Inert fatty materials*:** (5%-75%) Edible, inert fatty material having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.Effervescent agents:*** They are commonly used with acidic agents to cause a reaction that produces carbon dioxide. The carbon dioxide leads to a fizzing of the effervescent powder. Eg.Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine**).**

Release rate accelerants: (5%-60%) The release rate of the medicaments form the formulation can be modified by including Excipients.Eg.lactose, mannitol.

Release rate retardants: (5%-60%) Insoluble substances decreases the solubility and hence the release of medicaments. eg.Dicalciumphosphate,talc, magnesium stearate.

Buoyancy increasing agents: (upto80%) Materials which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. eg.Ethyl cellulose.

Low density material:Polypropylene foam powder (AccurelMP 1000).

TYPES OF FDDS

***Single unit floating drug delivery systems*:** Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract[40].

***Multiple unit floating drug delivery systems*:** Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple

unit systems avoid the 'all-or-none' gastric emptying nature of single-unit systems. It reduces the intersubject variability in absorption and the probability for dose dumping is lower.[41]

PHARMACOKINETIC AND PHARMACODYNAMIC ASPECTS OF FDDS:[42]

The aim of this section is to delineate these aspects in order to suggest rational selection of drugs for which FDDS would be a beneficial strategy.

PHARMACOKINETIC ASPECTS:

1. Absorption window
2. Enhanced bioavailability
3. Enhanced first pass biotransformation
4. Improved bioavailability due to reduced P-glycoprotein (P-GP) activity in the duodenum
5. Reduced frequency of dosing
6. Targeted therapy for local ailments in the upper GIT

PHARMACODYNAMIC ASPECTS OF FDDS:

1. Reduced fluctuations of drug concentration:
2. Minimized adverse activity at the colon:

6. EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

***Size and Shape Evaluation*:** The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability.[43]

***Floating Properties*:** Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design.[44]

***Floating lag time and total floating time determination*:** The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the flotation time.

***Surface Topography*:** The surface topography and structures were determined using scanning electron microscope operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM) and contact profiliometer. [45]

***Swelling Studies*:** Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques. The swelling studies by using Dissolution apparatus was calculated as per the following formula .[47]

Swelling ratio = Weight of wet formulation / Weight of formulations

***Determination of the Drug Content*:** Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by using HPLC, HPTLC methods, near infrared spectroscopy (NIRS) and also by using spectroscopy techniques.[48]

***Percentage Entrapment Efficiency*:** Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrapment efficiency was determined by using three methods such as Micro dialysis method, Ultra centrifugation, and pressure Ultra filtration.[49]

***In-Vitro Release Studies*:** In vitro release studies were performed to provide the amount of the drug that is released at a definite time period. Release studies were performed by using Franz diffusion cell system and synthetic membrane as well as different types of dissolution apparatus.[50]

***Powder X-Ray Diffraction*:** X-ray powder diffraction is the predominant tool for the study of poly-crystalline materials and is eminently suited for the routine characterization of pharmaceutical solids.[50]

Stability studies: The best formulation was kept for stability studies in a chamber (thermo lab) for a period of three months at temperature 40ºC±2ºC and RH 75±5%. The changes in physical appearance, weight, drug content, in-vitro drug release was observed after intervals of one month.[51]

ADVANCEMENT IN FLOATING DRUG DELIVERY SYSTEM:

Present scenario reflects many techniques to increase the retention time of drug in stomach but the present techniques which are available have some disadvantages i.e only floating system will be affected by the amount of fluid available in stomach. If the volume of fluid inside the stomach decreases than the floating systems will fail. So to increase the efficiency of floating drug delivery system now a day's combination techniques are used for example Floating Mucoadhesive drug delivery systems (FMDDS). Presently many research works are going on FMDDS. Out of which some are listed below:

Vikram Kumar Sahu et al. (2017), Formulated and evaluated floating-mucoadhesive microspheres of novel natural polysaccharide for site specific delivery of ranitidine hydrochloride by using Polysacharide extract from seeds of plant *Tamarindus indica* (TI) as mucoadhesive agent and edragit as release controlling polymers by using emulsion crosslinking method and concluded that the size of microspheres was in the range of 5.38 to 7.84 µm. SEM images revealed that all batches were spherical in size with smooth surface. Encapsulation efficiency was found to be decreased by decreasing the concentration of polysaccharide.[59]

Hakim Bangun et al. (2016) , Prepared and Evaluated a Floating-Mucoadhesive Alginate Beads as Gastroretentive Drug Delivery System of Antacids: The aim of this study was to prepare floating-mucoadhesive beads containing antacids that could float and adhere in stomach to prolong retention time of antacids and to determine the healing effects of antacids by using the sodium alginate, aluminium

hydroxide, magnesium hydroxide and liquid paraffin and concluded that the prepared Beads had no floating lag time and beads could stay floating for more than 12 hours. On buffering action test, beads containing 1.35% alginate could maintain the pH at 3.0 to 3.7 for 9hours, the mucoadhesive values was 58.73±0.05 dyne and the swelling index was 31.08±7.2.[60]

Jayvadan K. Patel et al. (2010), Formulated and evaluated glipizide floating-bioadhesive tablets.The purpose of this study was formulation and in vitro evaluation of floating-bioadhesive tablets to lengthen the stay of glipizide in its absorption area. Effervescent tablets were made using chitosan (CH), hydroxypropyl methylcellulose (HPMC), carbopolP934 (CP), polymethacrylic acid (PMA), citric acid, and sodium bicarbonate. Tablets with 5% effervescent base had longer lag time than 10%. The type of polymer had no significant effect on the floating lag time. All tablets floated atop the medium for 23-24 hr. Increasing carbopolP934 caused higher bioadhesion than chitosan ($p < 0.05$). All formulations showed a Higuchi, non-fickian release mechanism. Tablets with 10% effervescent base, 80% CH/20% HPMC, or 80% CP/20% PMA seemed desirable.[61]

Mukopadhyay et al. (2010), designed floating mucoadhesive tablet of Ciproflaxacin HCl by direct compression technique using polymer HPMC, SCMC, Carbopol in different ratios here effervescence base was prepared with sodium bicarbonate and citric acid and shown that tablet with 5% effervescent base has good controlled release over 10% of base. [62]

Belgumwar et al. (2009), prepared atenolol floating and bioadhesive drug delivery system using non effervescent agents. They used psyllium husk and HPMC K15M as rate controlling polymer to optimize the drug release up to 12hrs. And the prepared tablets were evaluated for various evaluation properties like tablet appearance, flow properties, *in-vitro* drug release, swelling characteristics, *ex-vivo* bioadhesive strength. [63]

7. CONCLUSION

One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastro-retentive dosage forms that will provide us with new and important therapeutic options. The floating drug delivery systems were designed in an effort to increase the gastric retention time of the dosage form and to control drug release. Floating matrix tablets were designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. 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. FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins,cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI Tract and whose development has been halted due to lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin,vasopressin, insulin, low molecular weight heparin,and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics.

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Conflict of Interest: None
Source of Funding: Nil