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Review article *Drug Delivery System*

Floating Drug Delivery Systems: A Comprehensive Review of Formulation Strategies and Applications

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ABSTRACT

Floating drug delivery systems (FDDS) have garnered significant attention in pharmaceutical research due to their ability to improve drug bioavailability and therapeutic efficacy. This comprehensive review aims to provide an in-depth analysis of the formulation strategies and applications of floating drug delivery systems.The review commences by discussing the physiological basis of gastric retention, highlighting the importance of FDDS in achieving prolonged residence time within the stomach. It explores the factors affecting gastric emptying and their impact on FDDS performance. Various approaches for formulating buoyant drug delivery systems, including single-unit and multiple-unit systems, are elucidated along with their respective advantages and limitations.Furthermore, the review delves into the diverse range of polymers, gelling agents, and gas-generating agents employed in FDDS formulation. Special emphasis is placed on recent advancements in material science and their contribution to enhancing the floating properties, drug release kinetics, and overall performance of these systems. Additionally, the integration of innovative technologies such as microbubbles, magnetic particles, and mucoadhesive polymers is explored for their potential to further optimize FDDS functionality.The applications of FDDS go beyond improving drug delivery to include therapeutic areas such as gastroesophageal reflux disease, peptic ulcers, motion sickness, and local gastric treatment. The review highlights the clinical significance of FDDS in these contexts, shedding light on recent clinical trials and outcomes.In conclusion, this review underscores the profound impact of floating drug delivery systems on pharmaceutical research and patient care. It provides a comprehensive understanding of the formulation strategies, materials, and applications associated with FDDS, paving the way for continued innovation in drug delivery and therapeutic effectiveness.

Keywords: Floating drug delivery systems, gastric retention, formulation strategies, buoyant systems, drug release kinetics, polymers, clinical applications.

INTRODUCTION

Novel drug delivery system

An oral drug delivery system that provides uniform drug delivery can only partially meet therapeutic and biopharmaceutical needs because it does not account for site-specific absorption rates within the gastrointestinal tract. As a result, designing delivery systems that release the drug at an appropriate time, at the appropriate site, as well as the desired rate is required.

Supply of drugs at the proper spot means, on the one hand, delivering locally efficacious pharmaceuticals such as antibiotics, anti-inflammatory drugs, or cryostatic agents at their target site, and on the other, releasing drugs with a limited absorption window such as Digoxin, Ampicillin, Cefuroxime axetil, and so on.

Delivering drugs molecules at the appropriate moment involves avoiding constant plasma levels for medicines that acquire tolerance, such as organic nitrates, or that have biorhythmic based action profiles, such as corticosteroids or antiasthmatic agents. In this instance, the drug delivery system must guarantee that drug-free and effective plasma levels are not altered.

Absorption of drugs at the appropriate pace involves reaching the optimum plasma level in an acceptable short period, avoiding excess in the case of rapidly absorbed drugs, and keeping up effective plasma levels during the specified time. Although the intensity of the pharmacological effect is proportional to the drug concentration at the site of action, which is proportional to the plasma drug concentration, an ideal situation is achieved when the amount of drug remains constant between the minimum effective and maximum safe levels (Therapeutic index). Controlled release dosage forms encompass a wide range of extended action formulation that provide sustained release of the active components at a specified rate and duration. The primary purpose of developing these systems is to provide a longer duration of effect and hence ensure more patient compliance. Pharmacokinetically, it is generally preferable to deliver a single dosage of medication that releases the active component over time rather than a series of doses at regular intervals.[1]

Gastro retentive drug delivery system

The oral means for administration is the most common and convenient method of drug delivery. For dosage forms intended for oral administration, the benefits of long-term delivery technology have yet to be completely realized. This is mostly because the extent of drug absorption from the GIT is dictated by GI physiology, regardless of the device's control release qualities. Although variable absorption from different sections of the GI has been recognized for decades, drug delivery devices to target medications to other regions of the GIT have recently been developed. Examples are gastro-retentive systems, delayed release systems, and colon targeting.

The goal of a controlled medication delivery system should be to achieve predictable and enhanced drug bioavailability. Several physiological challenges, such as the inability to limit and localise the DDS within desirable parts of the GI tract and the extremely changeable nature of the gastric emptying process, prevent the development process. The emptying process can take anywhere from a few minutes to 12 hours, depending on the subject's physiological state and the nature of the medicinal formulation. In humans, the relatively short gastric emptying period, which generally averages 2-3 hours across the main absorption zone (stomach or upper part of the intestine), can result in partial drug release from the DDS, resulting in decreased efficiency of the supplied dose. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drug with a stability problem. Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have lead to the development of oral controlled release dosage forms possessing gastric retention capabilities.

The fundamental challenge in developing oral controlled release dosage forms is not only to extend drug administration for more than 12 hours, but also to extend the presence of dosage forms in the stomach or someplace in the upper small intestine. dose forms with extended stomach residence duration (GRT), also known as gastro remaining or gastro retentive dose form (GRDF), will provide new and crucial therapeutic possibilities.For example, this will greatly lengthen the time span over which medications can be released, hence extending dosing intervals and increasing patient compliance beyond and above the compliance level of current controlled release dosage forms.[2]

GRDF will additionally significantly enhance stomach pharmacotherapy by causing local drug release, resulting in high drug concentrations at the gastric mucosa that are sustained over time. As an example, the eradication of Helicobacter pylori, which requires the consumption of various drugs several times per day according to a complicated regimen and frequently fails due to insufficient patient compliance, may be more reliably achieved using GRDF to administer smaller doses of medication for fewer times.

In the end, GRDF will be employed as a carrier for medications with absorption windows; these chemicals are only absorbed from very precise areas of the gastrointestinal mucosa, generally in the small intestine. Conventional controlled release dosage forms pass through the absorption window while still containing a considerable and somewhat unclear component of the dose, which is thus lost for absorption. An suitable GRDF, on the other hand, would gently release the entire dose across its prescribed GRT, making it continually available to the relevant tissue regions for absorption. There are two causes for the need for gastro retention.

- To enhance the bioavailability of medications such as cyclosporine, ciprofloxacin, cefuroxime axetil, ranitidine, and others that are absorbed mostly from the upper section of the GI tract and/or degraded in basic pH.
- In cases of gastrointestinal diseases, for local actionabsorption.

There are two causes for the need for gastro retention.

Gastric RetentionApproaches[3]

Floating drug delivery System (Low Density Approach)

These are also referred to as hydrodynamically balanced systems. (HBS/FDDS) They have a lower bulk density than stomach fluid, i.e. a bulk density less than one.

According to the "DocumentaGeigy," the specific gravity of gastric fluid is around 1.004 - 1.010 g/cm3, and hence the FDDS remains buoyant in the stomach for an extended period without changing the gastric emptying rate.While the system is floating on the gastric contents, the medicine is gently removed from the system at the desired rate. The residual system is discharged from the stomach once the medication is released.

To enable them to float, some scientists have created shells of polymers with densities lower than that of gastrointestinal fluid. Watanable et al. created a floating system using empty globular shells with a density lower than that of gastrointestinal fluid. This allowed the shells to float on the

gastric fluid and stay in the stomach for a longer period. Polymers such as polystyrene were used.

High density systems

High density formulations include coated pellets that have density greater than that of stomach contents. (~1.004g/cm^3) This is accomplished by coating the drug with heavy inert materials such as barium sulfate, titanium dioxide, iron powder or oxide. The weighted pellet can then be covered with a diffusion-controlling polymer membrane.

Swelling and expanding systems

Swelling type dosage forms are such that after swallowing, these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. Thesesystems may be referred to as 'plug type' systems since they exhibit tendency to remain lodged at the pyloric sphincter.

Bio-adhesive systems

They are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. It makes use of bio- adhesive polymers. These polymers tend to form hydrogen and electrostatic bonds at the mucus polymer boundary.

Modified- shape systems

These are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the GRT depending on size, shape and flexural modulus of the drug delivery system.

Use of other delayed gastric emptying devices

It includes sham feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release.

Osmotic Regulated System

It is comprised of an osmotic pressure-controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastricosmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure-controlled drug delivery device consists of two components: drug reservoir compartment and osmotically active compartment.

Incorporation of passage delaying food agents

The food excipients like fatty acids, e.g. salts of myrestic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.

Ion Exchange Resin

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin, resultant beads were then encapsulated in a semipermeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach and exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in a membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast the uncoated beads, which will sink quickly.

Criteria for selection of drug candidate for GRDF

- Absorption from upper GIT:

Drugs have a particular site for maximum absorption, e.g. Ciprofloxacin, whose maximum absorption is in the stomach only. The absorption of Metformin HCL is confined to the small intestine only and the conventional sustained release dosage forms may be poorly bioavailable since absorption appears to diminish when the dosage form pass into large intestine.

- Drugs having low pKa, which remains unionized in stomach for better absorption.
- Drugs having reduced solubility at higher pH, e.g. Captopril and Chordiazepoxide.
- Local action as it seen in the treatment of *Helicobacter pylori* by Amoxicillin[4].
- The bioavailability of drugs that get degraded in alkaline pH can be increased byformulating gastro-retentive dosage forms, e.g. Doxifluridine, which degrades in small intestine.
- To minimize gastric irritation which may be sudden increase of drug concentrationin the stomach, e.g., NSAID.

Hydrodynamically balanced system (fdds)

Principle

Floating dosage form is also known as hydrodynamically balanced system (HBS). It is an oral dosage form (capsule or tablet) that is designed to prolong the residence time of the dosage form within the GI tract. It is formulation of a drug and gel forming hydrocolloids meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also does so in an area of the GI tract that would maximize drug reaching its absorption site in solution and hence ready for absorption. Drug dissolution and release from the capsule retained in stomach fluids occur at the stomach, under fairly controlled condition. The retentive characteristics of the dosage form in gastric content are most significant for drugs.[5]

Insoluble in intestinal fluid.

That acts locally.

That exhibits site-specific absorption.

Design and Fabrication of FDDS[6]

Non effervescent FDDS

Colloidal gel barrier systems

Hydro dynamically balanced system (HBS™) of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids [for e.g. hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC), polysaccharides and matrix forming polymers such as polycarbophill,polyacrylates and polystyrene incorporated either in tablets or capsules. When such a system comes in contact with the gastric fluid, the hydrochloride in the system hydrates and forms a colloidal gel barrier around its surface. This gel barrier controls the rate of the fluid penetration into the device and consequent release of drug from it.

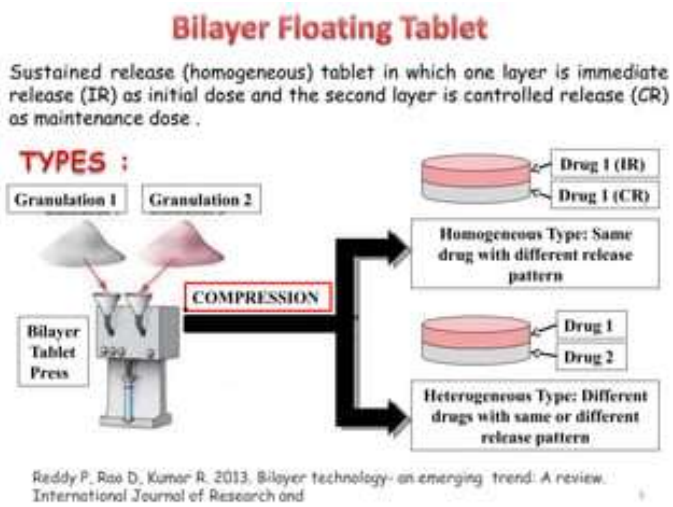
As the exterior surface of the dosage form goes in to the solution, the adjacent hydrochloride layer becomes hydrated and thus maintains the gel layer. The air trapped inside the swollen polymer maintains the density less than unity and confers buoyancy to these dosage forms.

The HBS must comply with following three major criteria:

1. It must have sufficient structure to form cohesive gel barrier.
2. It must maintain an overall specific density lower than that of gastric contents.
3. It should dissolve slowly enough to serve as reservoir for the delivery system.

A bilayer tablet can also be prepared to contain one immediate release and other sustained release layer. Immediate release layer delivers the initial dose whereas sustained release layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in system with bulk density lesser than that of gastric fluid and allows it to remain buoyant in the stomach for an extended period of time.

A multi-layer, flexible, sheath-like device buoyant in gastric juice showing sustained release characteristics has also been developed. The device consists of at least one dry self-supporting carrier film made up of water insoluble polymer matrix having a drug dispersed/dissolved therein, and a barrier film overlaying the carrier film. Both carrier and barrier films are sealed together along their periphery and in such a way as to entrap a plurality of small air pockets, which bring about the buoyancy to the laminated films.



Micro porous compartment system

This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with undissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

Intra-gastric floating and sustained release granules of Diclofenac sodium were developed using hydroxypropyl cellulose, ethyl cellulose and calcium silicate as floating carriers which had a characteristically porous structure with numerous pores and a large individual pore volume. The coated granules acquired floating ability from the air trapped in the pores of calcium silicate when they were coated with a polymer.[1]

Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter were prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing a precipitation of calcium alginate. These beads were then separated; snap frozen in liquid nitrogen and freeze-dried at – 40^0C for 24 hours, leading to formation of porous system that maintained floating force for over 12 hrs. They were compared with non-floating solid beads of same material. The latter gave a short residence time

of 1 hour, while floating beads gave a prolonged residence time of more than 5.5 hours.

Floating systems comprising of calcium alginate core separated by an air compartment from a membrane of calcium alginate or a calcium alginate/polyvinyl alcohol (PVA) have also been developed. The porous structure generated by leaching of PVA (water soluble additive in coating composition) was found to increase membrane permeability and thus preventing the collapse of air compartment.[7]

Hollow microspheres

Hollow microspheres (micro balloons), loaded with ibuprofen in their outer polymer shells were prepared by novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 40° C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in micro sphere of polymer with drug (Figure No. 6). These micro balloons floated continuously over surface of acidic solution media that contained surfactant, for greater than 12 hours.[8]

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. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts.[9]

Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber which contains a liquid e.g. ether or cyclo-pentane that gasifies at body temperature to cause the inflation of the chamber in the stomach. These devices are osmotically controlled floating systems containing a hollow deformable unit that can be converted from a collapsed to an expanded position and returned tocollapsed position after an extended period. A deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bioerodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach.[10]

Intra-gastric, osmotically controlled drug delivery system consists of an osmotic pressure controlled drug delivery device and an inflatable floating support in bio erodible capsule. When the device reaches the stomach, bioerodible capsule quickly disintegrates to release the drug delivery system. The floating support is made up of a deformable hollow polymeric bag containing a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled part consists of two compartments, a drug reservoir compartment, and an osmotically active agent-containing compartment. The drug reservoir compartment is enclosed in a pressure responsive collapsible bag, which is impermeable to vapors and liquid, and has a drug delivery orifice. The osmotic compartment contains an osmotically active salt, and is enclosed within semi permeable housing. In stomach, water is absorbed through the semi permeable membrane into the osmotic compartment to dissolve the salt. An osmotic pressure thus created acts on collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and release the drug solution through the delivery orifice. The floating support also contains a bioerodible plug that erodes after a predetermined time to deflate the support, which is then excreted from the stomach.

Gas generating systems

These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chyme. These tablets may be either single layered wherein the CO_2generating components are intimately mixed within the tablet matrix or they may be bilayer in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in outer layer for sustained release effect.

Multiple unit type of floating pills that generate CO_2, have also been developed. The system consists of sustained release pill as a seed, surrounded by double layer. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is swellable membrane layer. These kinds of systems float completely within 10 minutes and remain floating over an extended period of 5-6 hours.[11]

Stages of floating

(a) Conventional SR pills.
(b) Effervescent layer.
(c) Swellable layer.
(d) Expanded swellable membrane layer.
(e) Surface of water in the beaker (37 °C)

Table 1: Examples of various FDDS

Sr.No	Dosage Form	Drugs
1	Microspheres	Aspirin, Grisiofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast.
2	Granules	Diclofenac Sodium, Indomethacin, Prednisolone.
3	Films	Cinnarazine.
4	Powders	Several basic drugs.

5	Capsules	Chordiazepoxide HCL, Diazepam, Furosemide, L-Dopa, Benserazide, Misoprostol, Propranolol HCL, Ursodeoxycholic acid.
6	Tablets	Acetoaminophene, Acetylsalicylic acid, Amoxycillintrihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnarazine, Diltiazem, Flurouracil, Isosorbidemononitrate, Isosorbidedinitrate, Quinidine gluconate, Riboflavin-5'–phosphate, Sotalol, Theophylline, Verapamil HCL.

Limitations of FDDS

- The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
- The ability to float relies in the hydration state of the dosage form. In order to keep these tablets floating *In vivo*, intermittent administration of water (a tumbler full, every 2 hours) is beneficial.
- The ability of drug to remain in the stomach depends upon the subject being positioned upright.
- FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid.
- Drug like Nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be a desirable candidate for FDDS since the slow gastric emptying may lead to the reduced systemic bioavailability.

Mechanism of drug release from hydrophilic matrix

Early work in the erodible matrix tablets was done by **Lupidus (1967)**. This tablet differs from a common wax matrix tablet in two important ways; first, it offers a highly efficient dual release mechanism utilizing both diffusion and erosion to release the drug. Second, the tablet has a unique composition of polymers and minor amounts of inert ingredients.

The operative principle controlling drug release in the erodible matrix tablet is that on exposure to aqueous fluids, the tablet starts to partially hydrate to form a gel layer. An initial burst of soluble drug from the external layer may be released, followed by an expansion of the gel layer when water permeates into the tablet increasing the thickness of the gel layer and soluble drug diffuses the gel barrier. Concomitantly the outer layer become fully hydrated and dissolves, a process generally referred to as 'erosion'. Water continues to penetrate towards the tablet core until it has dissolved.[12]

For these equations to hold true:

- The drug release should be examined under near perfect sink conditions.
- The amount dissolved should be less than 30% of the initial dose.
- A pseudo steady state is maintained.
- Drug particles are quite small relative to the average distance of diffusion and areuniformly distributed in the matrix.

The diffusion coefficient remains constant and no interaction between the drug and the matrix occurs.

For water-soluble drugs release is affected by both diffusion of the matrix itself following hydration, a process known as attrition. Whereas an insoluble drug is released by exposure through erosion. These relationships indicate that the release of the drug is linear function of the $t_{1/2}$. In practice, it is often found that the linear relationship between the amount of drug released, and $t_{1/2}$ is only valid in part of the dissolution curve (75 – 80 % of the time needed for complete liberation of the drug).

The proposed process which could be rate determining in the release of drug from a system are:

- Permeation of the water,
- Gelation rate,
- The diffusion rate of the drug,
- The dissolution rate of the drug in the penetrating water.

Factors Influencing the Drug Release From Matrix

- Choice of matrix material
- Amount of drug incorporated in the matrix.
- Viscosity of the hydrophilic gums in aqueous system at a fixed concentration
- Drug: Matrix ratio
- Tablet hardness, porosity, density variation
- Entrapped air in tablet
- Tablet size and shape
- Drug particle size
- Solubility of drug in aqueous phase.

CONCLUSION

In conclusion, this review underscores the profound impact of floating drug delivery systems on pharmaceutical research and patient care. It provides a comprehensive understanding of the formulation strategies, materials, and applications associated with FDDS, paving the way for continued innovation in drug delivery and therapeutic effectiveness.

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