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A REVIEW ON FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention Floating Drug delivery system are designed to prolong the gastric residence time after oral administration, at particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Technological attempts have been made in the research and development of rate controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. Floating drug delivery systems have bulk density less than gastric fluids that have sufficient buoyancy to float over gastric contents and remain in stomach for longer duration of time without affecting gastric emptying rate and thereby improve the bioavailability of drugs. Floating dosage systems are one of the important technology in drug delivery systems which offers gastro retentive behavior and useful in the Treatment of gastrointestinal disorders such as gastro-esophageal reflux. Floating drug delivery system improve the bioavailability of drugs by improving drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating drug delivery 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 systems (FDDS), Gastric residence times (GRT), Gastric emptying times (GET), Bulk density, Bioavailability.

INTRODUCTION

Even though there are various advancement in drug delivery system, oral administration is most convenient and preferred route for the administration of drug in to the systemic circulation because of low cost therapy and ease of administration [1]. Oral controlled release drug delivery has gaining importance over conventional drug delivery because it is having control over drug release and maintains drug levels in the plasma within therapeutic level without offering any fluctuations for longer duration of time. Frequent dosing of drugs are required, if the drugs are having good absorption gastrointestinal tract (GIT) and have short half-lives because those drugs are eliminated rapidly from the systemic circulation. These drugs are suitable candidates for controlled drug delivery system which can release the drug slowly into gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a longer period of time. The drug delivery is in such a way that after oral administration of drug; the drug would be retained in the stomach and release the drug in a controlled manner so that the drug could be available for longer time its absorption sites [2].

All drugs are not absorbed uniformly throughout the gastrointestinal tract. Some drugs are absorbed uniformly throughout the gastrointestinal tract and some drugs are absorbed in a particular portion of gastrointestinal tract only (absorption window). Consequently incomplete absorption of drugs having absorption window especially in the upper part of the small

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intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed and some drugs have poor solubility in intestinal media. Oral controlled drug delivery system has two main draw backs: 1) limited gastric residence time (GRT), 2) varying gastric empting time; leads to incomplete drug release from the dosage form in absorption site and reduce the efficacy of administered dose, so a variety of techniques have been developed to prolong the gastric residence time by retaining the dosage form in the stomach.

One of the major challenges in the development of oral controlled drug delivery system is to modify the GI transit time. Gastric emptying of dosage forms is extremely unpredictable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times typically range between 5 minutes and 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and, hence, the transit of dosage forms. It is characterized by four phases: Phase I–Period of no contraction (40-60 minutes), phase II –Period of intermittent contractions (20-40 minutes), phase III–Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave. (10-20 minutes) and phase IV–Period of transition between phase III and phase I (0-5 minutes) [3].

There are several factors to consider for gastric retention of the dosage form like density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metclopramide, cisapride.) [4]. The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters [5].

This has led to the development of oral gastroretentive dosage forms. Gastroretentive drug delivery is an approach to prolong gastric residence time, by this means targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.

Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach [6], low density (floating) systems that causes buoyancy in gastric fluid [7, 8, 9], mucoadhesive systems that causes bioadhesion to stomach mucosa [10], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [11, 12], superporous hydrogel systems [13], magnetic systems [14] etc.

Suitable Drug Candidates for Gastro Retentive Delivery Systems

1. Drugs those are used in the treatment of local diseases e.g. peptic ulcers caused by H. pylori infections.
2. Drugs those are poor soluble in intestinal media and unstable in the intestinal pH. e.g. diazepam, verapamil HCl, captropril, ranitidine HCl.
3. Drugs that are having maximum absorption in stomach and upper part of GIT.
4. Drugs that disturb normal colonic microbial environment e.g. antibiotics against Helicobacter pylori.

FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems have bulk density less than gastric fluids that have sufficient buoyancy to float over gastric contents and remain in stomach for longer duration of time without affecting gastric emptying rate and release the drug slowly at a 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 fluctuations in plasma drug concentration (15).

Factors to be consider for formulation of floating drug delivery

1. It must maintain an overall specific gravity lower than that of gastric contents (1.004 – 1.010).
2. It should dissolve slowly and release contents slowly to serve as a reservoir.
3. It must form a cohesive gel barier.

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. Among these, the floating dosage forms have been most commonly used. 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 (given in the Figure 5(a)), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach.

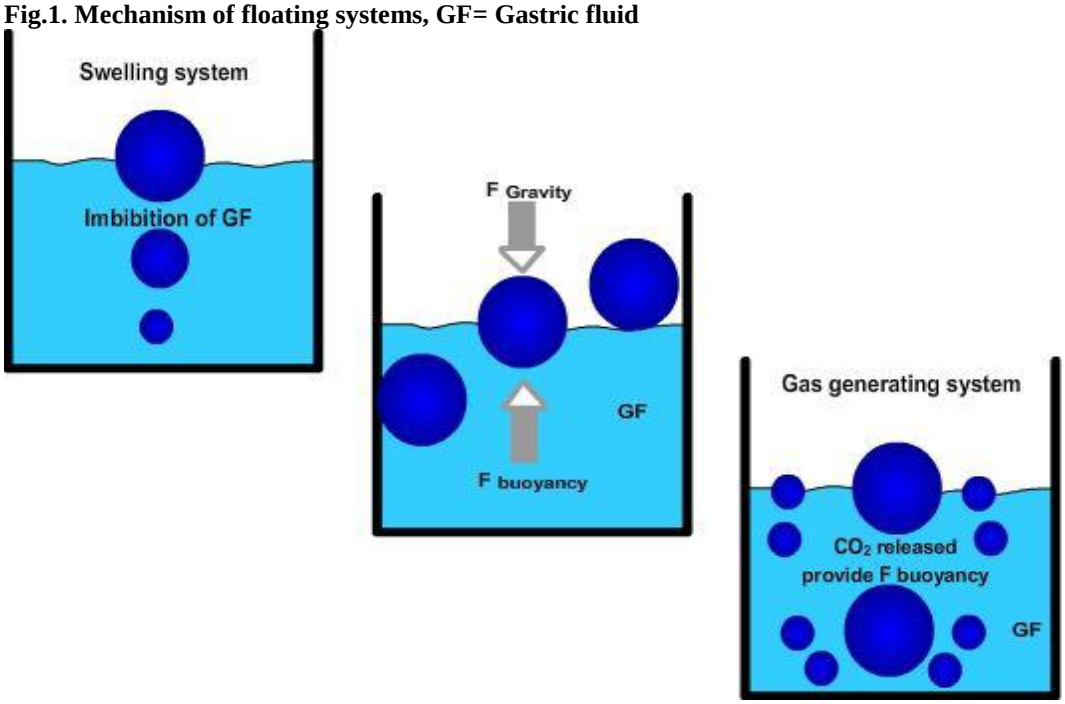
This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also

required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The 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 (Figure 5(b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations (16).

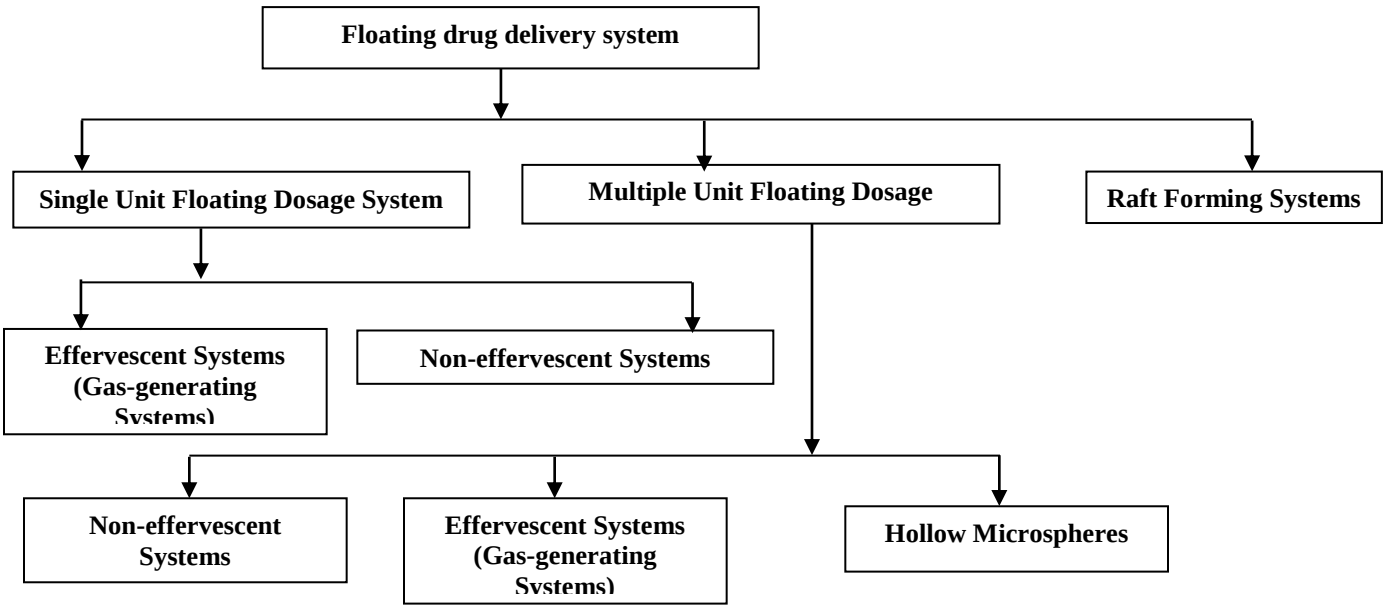
F = F buoyancy - F gravity
= (Df - Ds) gv--- (1)

Where, F= total vertical force, Df = fluid density,
Ds = object density, v = volume and
g = acceleration due to gravity

Fig.1. Mechanism of floating systems, GF= Gastric fluid



Based on the mechanism of buoyancy FDDS can be classified into



Effervescent systems

Effervescent systems are prepared with swellable polymers such as methyl cellulose or polysaccharides e.g. chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature. The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc [17]. In single unit systems, such as capsules or tablets [18] effervescent substances are incorporated in the hydrophilic polymer, and CO2 bubbles are trapped in the swollen matrix**.** In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 h. In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 h. Bilayer or multilayer systems have also been designed [19].

Non-effervescent systems

Excipients used most commonly in Non-effervescent systems are gel forming or highly swellable cellulose type hydro colloids, polysaccharides and matrix forming polymers such as hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. After swallowing non-effervescent system swells in contact with gastric fluids and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. When such system is comes in contact with an aqueous medium, hydrocolloid forms gel by hydrating, which controls the rate of diffusion of solvent in and drug out-of the system. As outer surface of the system goes into the solution, the immediate adjacent hydrocolloid layer becoming hydrated maintains the gel layer. As a result, the drug dissolves in and diffuse out with the diffusing the solvent, creating a reducing boundary within a gel structure [20]. This system can be further divided into four sub-types:

Hydrodynamically Balanced systems

These are the single unit dosage forms which contain one or more gel forming hydrophilic polymers. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice fora long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form [21]. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LP®, based on the system was marketed during the 1980's [22]. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile.

Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are 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 drug and carries the dissolved drug for continuous transport across the intestine for absorption.

Alginate beads

These are the multi unit floating dosage forms prepared from freeze-dried calcium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs [23].

Hollow microspheres / Microballons

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods [24]. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and

forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antiacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment as with Liquid Gaviscon\ (GlaxoSmithkline).

Evaluation of FDDS

The various parameters that need to be evaluated for their effects on GRT of buoyant formulations can mainly be categorized into following different classes:

Galenic parameters: Diametric size, flexibility and density of matrices.

Control parameters: Floating time, dissolution, specific gravity, content uniformity, hardness and friability (if tablets).

In case of multi particulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties

Geometrical parameters: Shape.

Physiological parameters: Age, sex, posture and food.

Test for buoyancy and in vitro drug release studies are carried out in simulated gastric and intestinal fluids maintained at 37^0C. Practically floating time is determined by using USP disintegration apparatus containing 900 ml of 0.1 N HCl as a testing medium maintained at 37^0C. Burns *et al* [25] developed and validated an *in vitro* dissolution method for a floating dosage form, which had both rapid release and SR properties. The method, although based on the standard BP (1993)/ USP (1990) apparatus 2 methods, was modified such that paddle blades were positioned at the surface of dissolution medium. The results obtained with this modified paddle method showed reproducible biphasic release dissolution profiles when paddle speeds were increased from 70 to 100 rpm and the dissolution medium pH was varied (6.0-8.0). The dissolution profile was also unaltered when the bile acid concentration in the dissolution medium was increased from 7 to 14 m *M*. The specific gravity of FDDS can be determined by the displacement method using analytical grade benzene as a displacing medium [26].

The system to check continuous floating behavior contains a stainless steel basket connected to a metal string and suspended from a sartorius electronic balance. The floating object is immersed at affixed depth into a water bath, which is covered to prevent water evaporation. The upward floating force could be measured by the balance and the data transmitted to an online PC through RS232 interphase using a sarto wedge program. A lotus- spread sheet could automatically pick up the reading on the balances. Test medium used in floating kinetics measurements was 900 ml simulated gastric fluid (pH 1.2) maintained at 37°C, data was collected at 30 sec interval; baseline was recorded and subtracted from each measurement. Dissolution basket had a holder at the bottom to measure the downward force.

γ-Scintigraphy

γ-Emitting radioisotopes compounded into CR-DFs has become the state-of-art for evaluation of gastroretentive formulation in healthy volunteers. A small amount of a stable isotope e.g. Sm, is compounded into DF during its preparation. The main drawbacks of γ-scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceuticals [27].

Radiology

This method is the state of art in preclinical evaluation of gastroretentivity. Its major advantages as compared to γ-scintigraphy are simplicity and cost. However, use of Xray has declined due to strict limitations, regarding the amount of exposure and it's often requirement in high quantity. A commonly used contrast agent is barium sulphate [28].

Gastroscopy

It comprises of peroral endoscopy, used with a fibereoptic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation [29].

Ultrasonography

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs [30]. Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, Ultrasonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.

Resultant weight test

An *in vitro* measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force F required to keep the object totally submerged in the fluid [31]. This force determines the resultant weight of the object when immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy (F bouy) and gravity (F grav) forces acting on the object as shown in the equation

F = F buoy – F grav
F = Df gV – Ds gV = (Df - Ds) gV
F = (Df – M / V) gV

In which F is the total vertical force (resultant weight of the object), g is acceleration due to gravity, Df is the fluid density, Ds is the object density, M is the object mass, and V is the volume of the object. By convention, a positive resultant weight signifies that the force F is exerted upward and that the object is able to float, whereas a negative resultant weight means that the force F acts downward and that the object sinks.

Advantages of Floating drug delivery system [32, 33]

1. The gastroretensive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
4. The gastroretensive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantages of floating drug delivery system

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.

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. A novel floating controlled-release drug delivery system was formulated in an effort increase the gastric retention time of the dosage form and to control drug release. FDDS promises to be a potential approach for gastric retention. Dosage forms with a prolonged GRT will bring about new and important therapeutic options. They will significantly extend the period of time over which drugs may be released and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing CRDFs. 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 gastroretentive dosage forms that will provide us with new and important therapeutic options. Floating matrix tablets are 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.

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