FLOATING DRUG DELIVERY SYSTEM - CHRONOTHERAPEUTIC APPROACH

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ABSTRACT
The purpose of writing this review on the floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. FDDS is one of the approaches in chronotherapeutic drug delivery. In the past reviews of FDDS the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, their classification and formulation aspects have been covered. This review summarizes the special focus on chronotherapeutics, diseases affected by biological rhythm, its importance, advantages, various approaches in Chronotherapeutic drug delivery and applications of FDDS. These systems are useful for several problems encountered during the development of a pharmaceutical dosage forms.

KEYWORDS: Floating drug delivery system, Chrono drug delivery system, Chronotherapeutics, and gastric retention.

INTRODUCTION
Over the past two decades, the pharmaceutical market has been demonstrated increasing preferably for controlled and targeted drug delivery system. Such systems have been focused on constant, variable; sustain drug release and/or targeting the therapeutic agent to a specific site/tissue/organ. However, recently there are certain conditions for which such release pattern is not suitable. Such conditions that lead to the requirements of a time programmed therapeutic system, which capable of releasing drug after predetermined time delay and maintain constant drug levels throughout the day. To date to increase the effectiveness of drug this chronotherapeutic drug delivery system is most preferable. Human circadian rhythm was based on sleep activity cycle, which is influenced by our genetic makeup and hence, affects the bodily functions day and night (24-hour period)¹. The numbers of hormones are released by the brain in the morning, while others are released during sleep. The dependence of bodily functions in certain disease states on circadian rhythm was well known. e.g. Blood pressure and heart rate were highest during 6.00 a.m. to 12.00 noon². Diseases such as hypertension, asthma, peptic ulcer, arthritis, etc were following the body's circadian rhythm³. This chronotherapeutic drug delivery system (CDDS) controls drug release according to circadian rhythms and the timing of symptoms. The term "Chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Many of the systems in human body like cardiovascular, pulmonary, hepatic and renal system show variation in their function throughout a typical day. This delivery system can release drug that will be characterized by a time period of no release (lag time) followed by a rapid and complete drug release.

CHRONOTHERAPEUTICS
Chrono therapeutics has unveiled a wristwatch-like device for the non-invasive automatic administration of drugs based on the amount and time instructed, thus improving patient compliance. Chrono dose were programmed like an alarm clock and worn like a watch to accurately deliver predefined-size doses to coincide with peak disease symptoms. This is important because hormones, neurotransmitters and other intra-body components are released in different amounts at different times of the day pursuant to daily patterns. Certain disease symptoms follow a daily pattern, with peak symptoms at certain times in the day. The drug effects can be optimized when administered in a varying dosage at predefined times. The current advances in chronobiology and chronotherapy for selected diseases suggest that “the one size fits all at all times” approach to drug delivery is no longer substantiated, at least for selected bioactive agents and disease therapy or its prevention.

Diseases influenced by biological rhythm
Many diseases are affected by the biological rhythm and show circadian symptoms intensity. Gout and peptic
ulcer attacks are most common at night (Sydenham, 1850)\(^2\). Acute pulmonary edema, congestive heart failure, and asthma were worsening nocturnally. Signs of allergic rhinitis and rheumatoid arthritis are stronger during the night or in the morning (at the time of wakening). Deadly pulmonary embolism, stroke and hypertensive crises were common to occur in the morning. Chronobiological studies have established circadian rhythm for almost all body functions e.g., heart rate, blood pressure, body temperature, and plasma concentration of various hormones, gastric pH and renal function\(^6\). It has become apparent that the rhythmic processes are indispensable for the treatment of human diseases. When the physiological functions are varying over time, the pathological states of disease are influenced due to circadian rhythms. Epidemiological studies have documented the elevated risk of disease symptoms during the 24-hour cycle (Fig.2)\(^7\).

**Adantages of CDDS**
Extended day time or night time activity, Reduced side effects, Reduced dosage frequency, Reduction in dose size, Improved patient compliance, Lower daily cost to patient due to fewer dosage units are required by the patient, Drug adapts to suit circadian rhythms of body functions or diseases, Drug targeting to specific site eg, Colon.

**Formulation optimization of chronotherapeutic drug delivery systems**
The single pulse or multiple pulse systems are the common system in which a rate delaying polymer is an imperative part of the formulation which are essential for providing the necessary lag time with a subsequent pulse release which may be time controlled or site specific. A basic chronotherapeutic system consists of a drug containing core and the approach is to prevent the drug release from the core during the initial hours by providing a barrier by using the polymer which slows the erosion or dissolution or swelling or rupture due to osmosis or may be the mechanism can be based on pH dependent solubility of the polymer as in methylethacrylates (MMA) to provide the necessary lag time. The polymers (non-exhaustive) employed for the purpose may be MMAs (Eudragit L-30 D 55, Eudragit R, S, RS, FS 30 D etc.), Polyvinyl acetate phthalate, hydroxypropyl methyl cellulose (Methocel E5, E15, E3, E50, K4M, K15M, K100LV, K100M), hydroxypropyl cellulose (HPC-L, HPC-M, HPC-H), ethyl cellulose with a pore former, polyvinyl alcohol (PVA), carnauba wax or bees wax with surfactant like polyoxyethylene monooleate (Tween 80), polyethylene oxide (PEOs), polyethylene glycol, carbopols etc. Once this barrier perishes or ruptures, the drug gets released in a pulse as in case of a single pulse system. A multiple pulse delivery unit may consist of a drug divided into 3-4 fractions in the form of pellets or minitabs one of which may be the immediate release fraction (uncoated IR fraction) for release in the stomach and the others may be delayed release fractions (coated with polymers meant for extending or delaying the release with different weight build up levels) customized to release the drug in other parts of the GIT. The pellets may be compressed in the form of a tablet with some disintegrant and may be filled inside a capsule shell to form a single unit system. Similarly the minitabs can be filled inside a capsule shell.

**Approaches for the chronotherapeutic drug delivery**
- Pulsatile delivery system
- Floating drug delivery system
- Enteric-coated systems
- Membrane diffusion controlled systems
- Osmotic systems
- Diffucaps/Surecaps Technology
- Compression coated system

**FLOATING DRUG DELIVERY SYSTEM**
Floating drug delivery system is one of the approaches in Chrono drug delivery system. 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. Later the residual system is emptied from the stomach. This results in an increased gastric retention time and a better control of fluctuations in plasma drug concentration\(^7\). Many buoyant systems have been developed in the form of granules, powders, capsules, tablets, laminated films and hollow microspheres. Gastro retentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract.

**Approaches to design floating dosage forms**
The following approaches have been used to design the floating dosage forms\(^8\).

**Single unit dosage forms**
In low density approaches\(^9\) the globular shells apparently having lower density than that of gastric fluid. The choice of the polymer can be either ethyl cellulose or HPMC. Depending on type of release desired. Finally the product floats on the gastric fluid by releasing the drug gradually over a prolonged duration. Fluid filled-floating
chamber type dosage forms includes incorporation of a gas filled floatation chamber in to a micro porous component that houses as a reservoir having apertures present at top and bottom walls through which the gastrointestinal fluid enters and dissolve the drug.

**Multiple unit dosage forms**

In spite of extensive research and development in the area of hydro dynamically balanced system (HBS) and other floating tablets, these systems suffer from an important drawback of high variability of the gastrointestinal transit time, when orally administered, because of their all-or-nothing gastric emptying nature. In order to overcome this, multiple unit floating systems were developed, which reduce the inter-subject variability in absorption and lower the probability of dose-dumping. The reports have described the development of both non-effervescent and effervescent multiple unit systems.

Much research has been focused in this and investigators are still exploring the field of hollow microspheres, capable of floating in the gastric fluid and having improved gastric retention properties.

**Classification of floating drug delivery system (FDDS)**

1. **Effervescent systems**
   
   **Gas generating system**
   
   These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). In single unit systems, such as capsules or tablets effervescent substances are incorporated in the hydrophilic polymer, and CO₂ bubbles are trapped in the swollen matrix. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers. Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO₂. The system was so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

Multiple unit systems floated completely within 10 min and 80% remained floating over a period of 5 h. In vivo studies have been carried out in beagle dogs and humans in the fed state using granules loaded with barium sulphate as a radio opaque marker. Most of it was floated in the stomach within 10 min and remained so for at least 3 h as observed by X-ray photography (Fig. 4).

**Low-density systems**

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/em³) with immediate buoyancy have therefore been developed. They are made up of low-density materials, entrapping oil or air. This multiple unit systems are called “microballoons” because of the low-density core. Foam-based floating micro particles were also developed consisting of polypropylene foam powder, drug (chlorpheniramine maleate, diltiazem HCl, theophylline or verapamil HCl) and polymer (Eudragit RS or polymethyl methacrylate). Based on a similar approach, a single unit floating system, (Fig 5) consisting of low-density polypropylene foam powder are developed which consists of matrix-forming polymers (HPMC, polyacrylates, sodium alginate, corn starch, carrageenan, agar, guar gum, and Arabic gum), drug and filler. All the tablets were remained floating for at least 8 hr in 0.1N HCl at 37°C. The release rate could effectively be modified by varying the matrix-forming polymer/foam powder ratio, the initial drug loading, the tablet geometry (radius and height), the type of matrix forming polymer, the use of polymer blends and the addition of water soluble or insoluble fillers (such as lactose or microcrystalline cellulose).

**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 when contact with gastric fluid. Formulations also typically contain antacids such as aluminum 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 gastro esophageal reflux treatment.

**Expandable systems**

Expandable gastro retentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and their sizes were increased due to swelling or unfolding processes that prolong their gastric retention time (GRT). After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastroretentivity was enhanced by the combination of...
substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach.

**Bio/Muco-adhesive systems**

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance the drug at a specific site. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarpohil, carbopol, lectins, chitosan and gliadin etc.

2. **Non-effervescent systems**

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polyethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid when it contact with gastric fluid after oral administration it will maintain a relative integrity of shape and a bulk density was less than unity within the gastric environment. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into the following sub-types.

**Hydrodynamically balanced systems**

Sheth and Tossounian were first designated these ‘hydrodynamically balanced systems’. These systems consist of drug with gel-forming hydrocolloids which will remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polycrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop this systems. The polymer was mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves after contacting with water followed by formation of a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. The continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form.

**Colloidal gel barrier system**

Hydrodynamically balanced 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 sites 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., hydroxypropyl cellulose, hydroxethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarpohil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

**Microporous compartment system**

This technology is based on the encapsulation of drug reservoir inside a Micro porous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the 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 apertures, dissolves the drug and carries for continuous transport across the intestine for absorption.

**Alginate beads**

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. 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 then separated, snap-frozen in liquid nitrogen and freeze-dried at 40°C for 24 h, leading to the formation of a porous system, which can maintain a floating force for over 12 h. These floating beads gave a prolonged residence time of more than 5.5 h.

**Hollow microspheres / Microballoons**

Hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres. The microballoons floated continuously over the surface of acidic media containing surfactant for greater than 12 hours in vitro.
Mechanism of floating system

Principle mechanism to achieve the gastric retention is floatation. 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 Fig. A), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is eliminated 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 effect, a minimal level of floating force \( F \) is also required to maintain the buoyance of the dosage form 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 a submerged object. The object floats better if \( F \) is on the higher positive side (Fig. B). This apparatus helps in optimizing FDDS with respect to stability and sustainability of floating forces produced in order to prevent any unforeseeable variations in intragastric buoyancy. 

\[
F = F_{buoyancy} - F_{gravity} = (Df - Ds) g v
\]

Where, \( F \) = total vertical force, \( Df \) = fluid density, \( Ds \) = object density, \( v \) = volume and \( g \) = acceleration due to gravity. Based on the buoyancy mechanism, FDDS can be classified into: (A) single unit floating dosage systems; (B) multiple unit floating dosage systems; (C) raft forming systems.

Applications of floating drug delivery system

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. The applications includes,

**Sustained Drug Delivery** eg. Sustained release floating capsules of nicardipine hydrochloride (8 h).

**Site-Specific Drug Delivery** eg, riboflavin and furosemide.

**Absorption Enhancement** LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

**CONCLUSION** Chronotherapeutics will certainly improve patient outcome and optimize disease management in the future. If the symptoms of a diseases display circadian variation, drug release will also be vary over time. Different technologies have been applied to develop time-controlled, pulsed, triggered and programmed drug delivery devices in recent years. Since it is seems that timing of drug administration during the therapy has significant impact upon treatment success. This chronotherapeutics is an important area for continuing the research. FDDS promises to be a potential approach for chronotherapeutics. This can provide sufficient gastric retention by which it provides sustained release at the peak time (during severity condition of the disease). In spite of its own limitations various efforts are being in progress to commercialize this drug delivery system.

**REFERENCES**

15. Streubel, A., Siepmann, J. and Bodmeier, R. Floating matrix tablets based on low density foam powder: effects of formulation


Table 1: List of drugs in the form of floating drug delivery systems

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Capsules</th>
<th>Microspheres</th>
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Table 2: Advantages and Disadvantages of Floating drug delivery system

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>1. Improved drug absorption</td>
<td>1. They are not suitable candidates for drugs with stability or solubility problem in stomach.</td>
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<tr>
<td>2. Controlled delivery of drugs</td>
<td>2. FDSS require sufficiently high level of fluid in the stomach so that the system can float and thus sufficient amount of water (200–250 ml) of water to be taken together with FDSS.</td>
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<tr>
<td>3. Delivery of drugs for local action in the stomach</td>
<td>3. Drugs having iritant effect on gastric mucosa are not suitable candidates for FDSS.</td>
</tr>
<tr>
<td>4. Minimizing the mucosal irritation</td>
<td>4. Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.</td>
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<td>5. Treatment of gastrointestinal disorders</td>
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<td>6. Simple and conventional equipment for manufacture</td>
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<td>7. Site-specific drug delivery</td>
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<tr>
<td>8. Ease of administration and better patient compliance</td>
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Fig No 1: Human circadian time structure (kalsbeek et al., 2006)^
Fig No 2: Diseases known to display circadian rhythm

Fig No 3: Gas-generating systems. Schematic monolayer drug delivery system (a). Bilayer gas-generating systems, with (c) or without (b) semi permeable membrane.

Fig No 4: Schematic representation of floating pill
Fig No 5: Schematic representation of structure of the low density, floating matrix tablets

Fig No 6: Schematic illustration of the barrier formed by raft forming system

Fig No 7: Mechanism of floating system