FLOATING DRUG DELIVERY SYSTEMS A REVIEW
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ABSTRACT
The recent developments of FDDS (Floating drug delivery system) including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

KEY WORDS: floating drug delivery systems (FDDS), single unit, multiple units, evaluation in vitro and in vivo.

1. INTRODUCTION
The oral route is considered as the most promising route of drug delivery (Debjit Bhomik, 2009). Effective oral drug delivery may depend upon the factors such as:
- Gastric emptying process
- Gastrointestinal transit time of dosage form
- Drug release from the dosage form and site of absorption of drugs

Most of the oral dosage forms possess several physiological limitations such as, Variable gastrointestinal transit because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed.

All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS) (Reddy, 2002).

The hydrodynamic balanced system (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions. Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior.

Drugs that could take advantage of gastric retention include eg: Furosemide, Cyclosporine, Allopurinol, Ciprofloxacin and Metformin.

Formulation of floating dosage forms
Floating microspheres: eg. Aspirin, griseofulvin, P-nitroaniline, Ibuprofen, Terfenadine and Tranilast.
Floating granules eg: Diclofenac sodium, Indomethacin and Prednisolone, films eg: Cinnarizine.
Floating capsules eg: Chloridiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, benserazide, Ursodeoxycholic acid and Pepstatin.
Floating tablets and pills: - eg: Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin Trihydrate, Atenolol, Diliazem, Fluorouracil, Isosorbide Mononitrate, Paraaminobenzoic acid, Piretamide, Theophylline and Verapamil hydrochloride, etc.

Excipients: Used most commonly in these systems include eg: HPMC, Polyacrylate polymers, Polyvinyl acetate, Carbopol, Agar, Sodium alginate, Calcium chloride, Polyethylene oxide and Polycarbonates (Desai, 1984).

Advantages of floating drug delivery system
- The principle of HBS can be used for any particular medicament or class of medicament
- The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate

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The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. Antacids. (Debjit Bhowmik, 2009)

- The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
- Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
- Certain types of drugs can benefit from using gastro retentive devices. These include:
  - Drugs acting locally in the stomach
  - Drugs those are primarily absorbed in the stomach
  - Drugs those are poorly soluble at an alkaline pH
  - Drugs with a narrow window of absorption
  - Drugs absorbed rapidly from the GI tract and
  - Drugs those degrade in the colon, (Chin, 1989)

Disadvantages of floating drug delivery systems

- There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
- Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
- Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

Approaches to gastric retention: Various approaches have been followed to encourage gastric retention of an oral dosage form

Hydrodynamically balanced systems (HBS): incorporated buoyant materials enable the device to float (Daggy, 2002).

Effervescent systems: Gas-generating materials such as sodium bicarbonate or other carbonate salts are incorporated. These materials react with gastric acid and produce carbon dioxide, which entraps in the colloidal matrix and allows them to float.

Low-density systems — have a density lower than that of the gastric fluid so they are buoyant.

Bioadhesive or mucoadhesive systems: These systems permit a given drug delivery system (DDS) to be incorporated with bio/mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying.

High-density Systems: sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Commonly used Excipients eg: Barium sulphate, Zinc oxide, Titanium dioxide and iron powder etc.

Large Single- unit Dosage Forms - These dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach. Permanent retention of rigid large-sized single-unit forms can cause bowel obstruction, intestinal adhesion and gas troplasty.

Co-administration of gastric- emptying drugs: This concept of simultaneous administration of a drug to delay gastric emptying together with a therapeutic drug has not received the favour of clinicians and regulatory agencies because of the questionable benefit-risk ratio associated with these devices.

Raft systems incorporate alginate gels — these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating of raft on gastric fluid.

Types of floating drug delivery systems (FDDS) Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

- Effervescent System, and
- Non-Effervescent System

Effervescent System: Effervescent systems include use of gas generating agents, carbonates (eg. Sodium bicarbonate) and other organic acid (eg. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) gas, 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.
These effervescent systems further classified into two types

- Gas Generating systems
- Volatile Liquid/Vacuum Containing Systems.

**Gas - Generating Systems:** Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS): The formulated by intimately mixing the CO₂ generating agents and the drug with in the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

**Intra Gastric Bilayer Floating Tablets:** These are also compressed tablet as shown and containing two layer i.e.,

- Immediate release layer and
- Sustained release layer.

**Multiple Unit type floating pills:** These system consist of sustained release pills as ‘seeds’ surrounded by double layers. The innerlayer consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then formsswollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO₂ within the system.

**Intragastic Floating Gastrointestinal Drug Delivery System:** These system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

**Inflatable Gastrointestinal Delivery Systems:** In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

**Intragastic Osmotically Controlled Drug Delivery System:** It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug device. The osmotic pressure controlled drug delivery device consist of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing.

**Non effervescent systems:** The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol.

The various types of this system are as:

**Single Layer Floating Tablets:** They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

**Bilayer Floating Tablets:** A bilayer tablet contain two layer’s one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

**Alginate Beads:** Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 hour.
Hollow Microspheres: Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloro ethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 400°C. (Debjit Bhowmik, 2009).

Methods for preparing floating dosage form
Following approaches can be used for preparing floating dosage forms:

- Using gel forming hydrocolloids such as hydrophilic gums, gelatin, algatines, cellulose derivatives, etc.
- Using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate. (Wilson and Washington, N, 2002)
- By reducing particle size and filling it in a capsule
- By forming carbon dioxide gas and subsequent entrapment of it in the gel network
- By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules
- By incorporation of inflatable chamber which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach.

The factors which govern the effectiveness of active medicaments in HBS are:

- Amounts of active medicament to produce therapeutic effect
- Bulk density
- Hydrophilic and hydrophobic properties
- Stability in gastric fluids

Evaluation of floating drug delivery systems
Various parameters that need to be evaluated in gastroenteric formulations include floating duration,
- Dissolution profiles
- Specific gravity
- Content uniformity
- Hardness and friability in case of solid dosage forms

In the case of multiparticulate drug delivery systems

- Differential scanning calorimetry (DSC)
- Particle size analysis, flow properties
- Surface morphology, and mechanical properties are also performed.

The tests for floating ability and drug release are generally performed in simulated gastric fluids at 37°C. It was given by the vectorial sum of buoyancy

F(b) and gravitational forces F(g) acting on the test object.

\[ F = F_b + F_g \]  

Equation 1 can be rewritten as,

\[ F = (d_f - d_s)gV = (d_f - w/v)gV \]  

where \( F \) is the resultant weight of the object, \( d_f \) and \( d_s \) represent the fluid density and solid object density, \( g \) is the acceleration due to gravity and \( W \) and \( V \) are the weight and volume of the test objects.

A typical floating kinetic curve was obtained by plotting floating force vs time and four parameters were used to describe the floating properties of the capsules from this graph: F max, T max, Fr, and AUC f.

Similar to Equation 2, the overall force that the capsule is subjected can be given by,

\[ F = (pm - pc)gVc \]  

where \( pm \) and \( pc \) are the density of floating media and test object, \( Vc \) is the volume of the test object.

In this equation, two parameters, \( pc \) and \( Vc \), are important for overall floating force. During the measurement of buoyancy, \( Vc \) increased due to swelling of polymer and \( pc \) increased due to water uptake.

Applications of Floating Drug Delivery Systems
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. These are summarized as follows.

Sustained Drug Delivery: HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo.

Site-Specific Drug Delivery: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the
duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased.

Absorption Enhancement: Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

2. CONCLUSION

Drug absorption in the gastrointestinal tract is highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. 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.

REFERENCES


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