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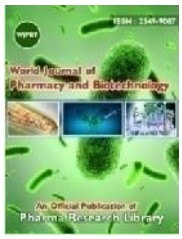

Review Article Open Access

Floating Drug Delivery Systems as Gastro retentive Drug Delivery Systems – A Review

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A B S T R A C T

Most of the orally administered dosage forms have several physiology limitations such as GI transit time, incomplete drug adsorption due to incomplete release of drug from the device and too short residence time of the dosage forms in the adsorption region of GIT. To overcome these limitations many attempts have been made by scientist by designing various drug delivery systems among these systems, floating drug delivery system is one of the approaches which remain buoyant due to their lower density that of the GI and Intestinal fluids, both single and multiple unit systems have been developed. Prolonged gastro retention of the therapeutic moiety may offer numerous advantages, including improvement of bio availability, therapeutic efficiency and possible reduction of dose. Floating drug delivery systems includes the various formulations like tablets, beads, microspheres etc., in this present review focusing the various types of formulations, formulation methods, polymers used, evaluation parameters and optimization methods used for developing the floating drug delivery systems

Keywords: Floating Drug Delivery System, Gastro retentive Drug Delivery System, Application.

A R T I C L E I N F O

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1. Introduction

Various devices such as muco adhesive, swelling, high-density and floating systems have been developed to increase GRT of a dosage form. These delivery systems can be either in single (fluid filled floating chamber) or multiple (microspheres) unit system. Single unit formulations are

associated with problems such as sticking and produce a serious problem of all or none release. Whereas multiple unit dosage forms are devoid of these disadvantages. Floating drug delivery system (FDDS) have low density and so float over the gastric contents it result the slow and controlled release of drug. Gastro retentive system (GRT) can remain in the gastric region for several hours and hence significantly prolong the gastric emptying time of the drug in the GIT. This system suitable for drugs having, locally active in the stomach eg. Misoprostol, Narrow absorption window in GIT eg. L-DOPA, unstable in the intestinal or colonic environment like captopril and metronidazole. Floating drug delivery system is under the category of sustained release products[1-6].

Sustained release dosage forms:

Sustained drug delivery system that is designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose." The basic goal of therapy is to achieve steady state blood level that is therapeutically effective and nontoxic for an extended period of time.

Advantage:

- Frequency of drug administration is reduced.
- Patients compliance can be minimized.

Disadvantage:

- Probability of dose dumping.
- Cost of single unit is higher.

Approaches to gastric retention system:

A. Floating systems
B. Bioadhesive systems
C. Swelling and expanding systems
D. High density systems
E. Incorporating delaying excipients
F. Modified systems

Floating systems:

These systems have low density and so float over the gastric contents

Bioadhesive systems:

They bind with stomach mucosa and hence, enable the localized retention of the system.

Swelling and expanding systems:

Such systems absorb water and hence, enlarged size.

High density systems:

They remain in the stomach for longer period of time, by sedimenting to the folds of stomach.

Incorporating delaying exciepients

Feeding of digestible polymers or fatty acid salts that change the motility pattern thereby decreasing the gastric emptying rate and prolongation of the drug release.

Modified systems: Non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends

2. Floating drug delivery system

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration[6-10]

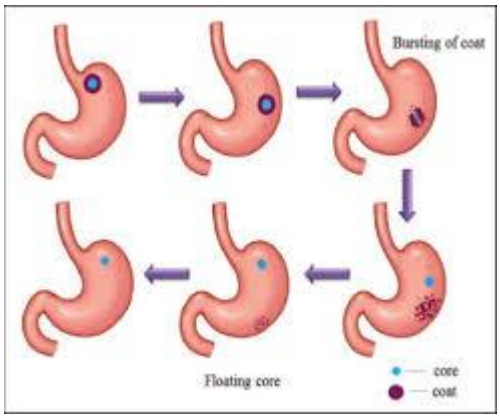
Classification of Floating Drug Delivery System

Non-effervescent System:

- Colloidal gel barrier system.
- Alginate beads.
- Hollow microspheres / Microballons.
- Intragastric Floating Drug Delivery Device / Microporous compartment system

Effervescent system:

- Gas generating system
- Volatile liquid containing system



A. Non-Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration 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 this dosage forms. The most commonly used excipient in non-effervescent floating drug delivery system are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polyacrylate, polymethacrylate and polycarbonate. After oral administration these dosage form swells in contact with gastric fluid and attains a bulk density of < 1 (Fig-1). The air entrapped within the swollen matrix imparts buoyancy to the dosage form[10-14].

I. Colloidal gel barrier systems

Hydrodynamically balance system (HBS). Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level (20-75%w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Poly sacchacarides and matrix forming polymers such as poly carbophil, polyacrylates and polystyrene, incorporated either in tablets

or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

II. Micro porous compartment systems

This technology is based on the encapsulation of drug reservoir inside a microporous 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 the dissolve drug for continuous transport across the intestine for absorption.

III. Multi particulate system:

Multiple 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 a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, leading to the formation of porous system, which can maintain a floating
force over 12 h.

Also called Floating Beads.

- Administered through oral dosage forms.
- Each exhibiting some desired characteristics.
- Dosage of the drug substances is divided on a plurality of subunit.
- Spherical particles with diameter of 0.05-2.00mm.
- Active substance is a number of small independent subunits.
- Subunits are filled into a sachet.

IV. Micro balloons:

- Hollow microspheres are also known as microballoons. Hollow microspheres are prepared by emulsion solvent diffusion method. In this method a solution or dispersion of drug and polymer is prepared in solvent (like dichloromethane, ethanol, isopropanol or a combination of these). This dispersion/solution is introduced into an aqueous solution of PVA (polyvinyl alcohol) forming an O/W type emulsion. This emulsion is agitated using propeller type agitator to remove the organic solvent, which produces the microballoons, size between 500-1000 mm. Controlled drug release fashions.
- Polymeric micro balloons as carrier for drugs.
- Hallow microspheres –micro balloons.
- Micro balloons were floatable in vitro for 12 hrs, when immersed in aqueous media.
- Radio graphical studies proved that micro balloons orally administered to human dispersed in the upper part of stomach retained there for three hrs against peristaltic movements.

(B) 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[15-21].

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, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a 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 systems from the stomach. Osmotically controlled floating systems containing a hollow deformable unit.

Two chambers in the system

- First chamber – drug
- Second chamber - volatile liquid.

II. Gas generating systems

Effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2 gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime. A multiple unit type –double layers, inner layer is an effervescent layer containing NAHCO3 and tartaric acid and outer layer is of a swellable membrane layer containing PVA, shellac etc. Effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed. Resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water, CO2 is released, causing the beads to float in the stomach. These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.31.

3. Formulation Aspects

Based on three important criteria

- Drug
- Delivery
- Destination.

Based on physiochemical properties

- Pka
- Ph
- Solubility
- Incompatibility.

Others

- Adsorption
- Biological half life
- Dose

Method of Formulation

- Materials Required
- Active ingredients

- Polymers
- Exciepients such as
- Binding agents
- Adsorbents
- Emulsifying agent
- Preservatives
- Others

Methods for Preparing Floating Dosage Form:

1. Using gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
2. Using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
3. By reducing particle size and filling it in a capsule.
4. By forming CO2 and subsequent entrapment of it in the gel network.
5. By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
6. 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.

Polymers in Floating Drug Delivery System

1. Polymers play an important role in Controlled drug delivery system.
2. FDDS is an approach to achieve drug release for long duration.
3. Acrylic polymers are widely used for the preparation of floating microspheres.

Selection of Polymeres

Synthetic polymers

Gas generating agents: Alkalinizing agents and acidulent, Sodium bicarbonate, Calcium carbonates, Citric acid, Tartaric acid, Adipic acid

A. **Viscolyzing agent**
   Sodium alginate, Carbopol 934
B. **Swelling agent / gel forming polymer**
   Hydroxypropyl methylcellulose (HPMC)
C. **Disintegrating agent**
   Povidone, Polyplasdone XL and XL-10

Natural Polymers

- Guar gum
- Chistosan
- Xanthan gum
- Psyllium husk starch
- Alginates

Some Drugs with Polymer Examples:

- Famotidine – Ethical k 15M, Methocel k 100M
- Theophylline – HPMC K 100M,Xanthan gum, Carbopol 934P, MCC
- Glipizide – HPMC, MC and EC
- Ranitidine HCL – HPMC 15cps and Eudragit E-100
- Cefuroxime axetil – HPMC and SLS
- Levofloxacin Hemihydrate – HPMC K 100M.

Advantages of FDDS

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.

Disadvantages of FDDS

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs to treat irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Importance of Floating Drug Delivery Systems

1. Enhance bioavailability
2. Sustained drug delivery
3. Site–specific drug delivery systems
4. Absorption enhancement
5. Minimize adverse activity at the colon
6. Reduce fluctuations of drug concentration
7. Evaluation of floating dosage forms

Pre Formulation Study[21-26]

Evaluation parameters:

Melting point determination, Solubility, Compatability test, Flow property of floating, granules, Angle of repose, Determination of bulk density and true density and Compress ability index

Pre-compression evaluation:

The granules were evaluated for flow property i.e. angle of repose, bulk density, tapped density, compressibility index (Carr's index) and Hausner's ratio using standard procedures

Post-compression evaluation:

Hardness, friability, assay, content uniformity (Tablets), Morphology study (size & shape), Floating lag time and total floating time, determination, Drug release, Weight gain and water uptake, x-ray/gamma scintigraphy, pharmacokinetic studies and specific gravity [9-14].

Factors Affecting Gastric Residence Time of FDDS:

A) Formulation factors:

- Size of tablets
- Density of tablets
- Shape of tablets
- Viscosity grade of polymer

B) Idiosyncratic factors:

- Gender
- Age
- Posture

- Concomitant intake of drugs
- Feeding regimen

Limitations of Floating Drug Delivery Systems

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

List of Drugs Explored For Various Floating Dosage Forms

Microspheres Tablets:

Chlorpheniramine maleate, Aspirin, griseofulvin, Acetaminophen, p-nitroaniline, Acetylsalicylic acid, Ibuprofen, Amox-ycillin trihydrate, Terfenadine, Ampicillin, Trani-last, Atenolol, Theophylline, Captopril, Isosorbide di nitrate, Sotalol, Isosorbidemononitrate.

Films: P-Aminobenzoic acid, Cinnarizine, Pireta-nide, Prednisolone, Quinidine gluconate.

Granules: Cinnarizine, Diclofenac sodium, Diltia-zem, Indomethacin, Fluorouracil, Isosorbidemononitrate, Isosorbide dinitrate, Prednisolone.

Powders: Riboflavin, Sotalol, Theophyl-line.

Capsules: Verapamil HCl, Chlordiazepoxide HCl, Diazepam, Furosemide, L-,opa and benserazide Misoprostol, Propranolol HCl, Ursodeoxycholic ac-id, Nicardipine .

4. Conclusion

Recently many drugs have been formulated as floating drug delivery systems with an objective of sustained release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer-mediated non effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half-life.

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