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Floating Microspheres: A Promising Drug Delivery

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M. Ishwarya[1], S. Ramu[*], K. Saravana kumar[2]

Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, A. Rangampet, Affiliated to JNTUA

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ABSTRACT

Floating microspheres are multiple unit drug delivery systems which are designed to obtain prolonged or controlled drug delivery to enhance bioavailability, stability and to target the drug to a specific site at a predetermined rate. A controlled drug delivery system with the prolonged residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. The main limitations are attributed to the inter and intra-subject variability of gastrointestinal (GI) transit time and to the non-uniformity of drug absorption throughout the alimentary canal. Floating or hydrodynamically controlled drug delivery systems are used in such applications. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Floating microspheres have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation. Such systems have more advantages over the single-unit dosage forms. The present review briefly addresses the physiology of the gastric emptying process with respect to floating drug delivery systems. The purpose of this review is to bring together the recent literature with respect to the method of preparation, and various parameters affecting the performance and characterization of floating microspheres.

INTRODUCTION:

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach without affecting 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 better control over fluctuations in plasma drug concentration.[1]

Comprehensive knowledge about GI dynamics such as gastric emptying, small intestine transit, colonic transit, etc. is the key for the designing of oral controlled release dosage forms. The rate and extent of drug absorption from different sites of GI tract and factors that govern the absorption further assist the design of dosage form.

Floating system

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach without affecting the gastric-emptying rate for a prolonged period.

Advantages of FDDS[2,3]:

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

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-oesophageal reflux.

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 that cause 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 diametric size. Therefore patients should not be dosed with floating forms just before going to bed.

TYPES OF FDDS:

Based on the mechanism of buoyancy, two distinctly different technologies i.e. non-effervescent and effervescent systems have been utilized in the development of FDDS:

1. Non-Effervescent FDDS.

2. Effervescent FDDS.

I. Non-Effervescent FDDS

The FDDS belonging to this class are usually prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharide or matrix forming polymers like polyacrylate, polycarbonate, polystyrene, and poly-methacrylate.[4]The drug in the dosage form dissolves in and diffuses out with the diffusing solvent forming a 'receding boundary' within the gel structure.[5]The various types of this system are as:

- Single Layer Floating Tablets
- Bi-layer Floating Tablets
- Alginate Beads
- Hollow Microspheres

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 maintains bulk density of less than unity.

Bi-layer Floating Tablets:

A bi-layer tablet contains two layers one immediate release layer which releases initial dose from a system while 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:

Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into the aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to the formation of the porous system, which can maintain a floating force for over 12 hours.

Hollow Microspheres:

Hollow microspheres (micro balloons), loaded with a drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The micro balloons floated continuously over the surface of acidic dissolution media containing the surfactant for more than 12 hours *in vitro*[6].

Fig 1: Hallow microsphere

II. Effervescent FDDS

The buoyant delivery system utilized matrices prepared with swellable polymers, such as Methocel or polysaccharides (e.g. chitosan) and effervescent components (e.g. Sodium

bicarbonate and citric acid or tartaric acid) or matrices having chambers of liquid that gasifies at body temperature.[7,8.]

These effervescent systems further classified into two types.

I. Gas Generating systems

II. Volatile Liquid/Vacuum Containing Systems.

1. Gas – Generating Systems:

Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System (HBS):

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. 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.

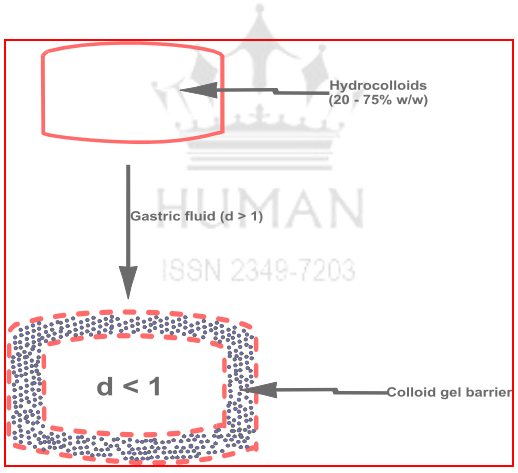

Fig 2: Intra Gastric Single Layer Buoyant Tablet

Intra Gastric Bi-layer Floating Tablets:

These are also compressed tablet and containing two layers i.e,

i. Immediate release layer and

ii. Sustained release layer.

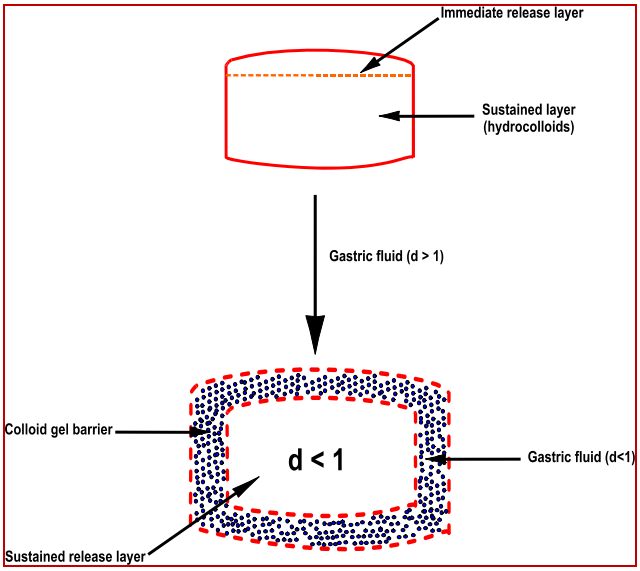

Fig 3: Intra Gastric Bi-layer Buoyant Tablet

2. Volatile Liquid / Vacuum Containing Systems:[9]

- Intra-gastric Floating Gastrointestinal Drug Delivery System
- Inflatable Gastrointestinal Delivery Systems
- Intra-gastric Osmotically Controlled Drug Delivery System

Intra-gastric Floating Gastrointestinal Drug Delivery System:

These systems 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.

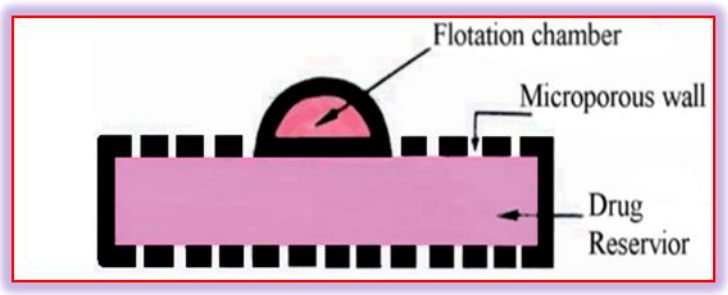

Fig 4: Intra-gastric Floating Gastrointestinal Drug Delivery Device

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.

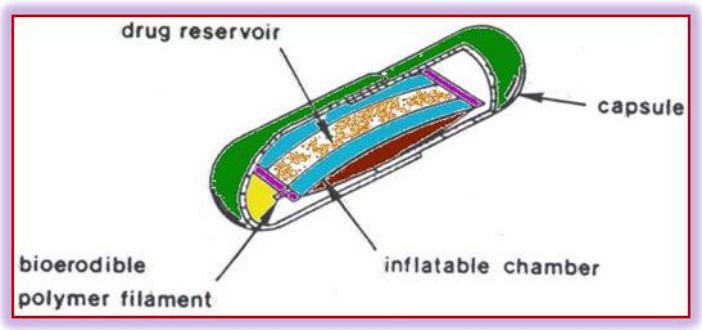

Fig 5: Inflatable Gastrointestinal Delivery System

Intra-gastric 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. The osmotic pressure controlled drug delivery device consists 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 vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing.

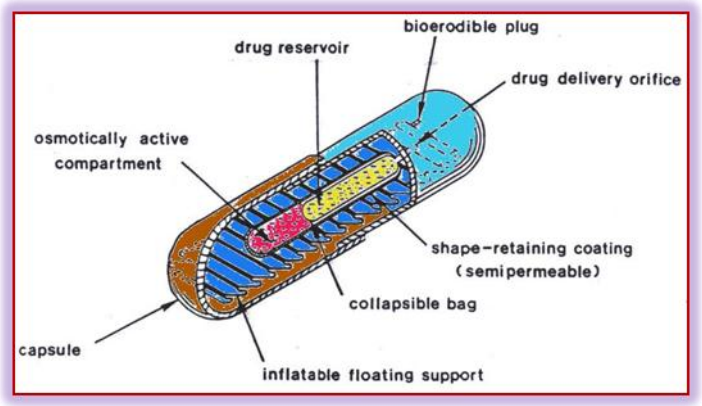

Fig 6: Intra-gastric Osmotically Controlled Drug Delivery System

METHODS OF PREPARATION OF FLOATING MICROSPHERES

- Spray Drying
- Solvent Evaporation
- Ionic gelation method
- Single emulsion technique
- Double emulsion technique
- Phase separation coacervation technique
- Spray drying and spray congealing
- Quasi emulsion solvent diffusion

Spray Drying[10]

In Spray Drying technique, the polymer is first dissolved in a suitable volatile organic solvent. The drug in the solid form is then dispersed in the polymer solution with high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100µm.

Solvent Evaporation[10,11]

The solvent Evaporation process is carried out in a liquid manufacturing vehicle phase. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. the core material mixture is dispersed in the liquid manufacturing vehicle phase with agitation to obtain the appropriate size microcapsule.

Ionic gelation method

In this method cross-linking agent & polymer alone or in combination with copolymers were dispersed in the purified water to form a homogeneous polymer mixture. The drug was added to the polymer dispersion and mixed thoroughly on a magnetic stirrer to form a homogeneous

dispersion. The gelation medium was prepared by dissolving calcium chloride in 2% glacial acetic acid. The homogenous alginate solution was extruded using syringe needle into the gelation medium. Then, microsphere was collected and washed with distilled water twice, dried at room temperature for 24 hr.

Single emulsion technique

The natural polymers are dissolved or dispersed in the aqueous medium followed by dispersion in the non-aqueous medium like oil. In the next step, the cross-linking of the dispersed globule is carried out. The cross-linking can be achieved either by means of heat or by using the chemical crosslinkers.

Double emulsion technique

Double emulsion method involves the formation of the multiple emulsions or the double emulsion type w/o/w and is best suited for water-soluble drugs, peptides, proteins and the vaccines. The continuous phase has generally consisted of the polymer solution that eventually encapsulates the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization results in the formation of a double emulsion.

Phase separation coacervation technique

In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes the first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of a polymer. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates.

Spray drying and spray congealing[12,13]

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying leads to the formation of porous microparticles.

Quasi-emulsion solvent diffusion

Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase consists of drug, ethanol, and polymer. At first, the internal phase is manufactured at 60ºC and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40ºC for a day.

EVALUATION OF FLOATING MICROSPHERES[14, 15, 16, 17]

1. Particle size and shape: The most widely used procedures to visualize microspheres are conventional light microscopy (LM) and scanning electron microscopy (SEM).

2. Electron spectroscopy for chemical analysis: The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA).

3. Density determination: The density of the microspheres can be measured by using a multi-volume pycnometer.

4. An angle of contact: The angle of contact is measured to determine the wetting property of a microparticulate carrier.

5. *In vitro* methods: Release studies for the different type of microspheres are carried out by using different suitable dissolution media, mostly by Type 1 apparatus (USP / BP).

6. Drug entrapment efficiency: Drug entrapment efficiency can be calculated by following equation, % Entrapment = Actual content/Theoretical content x 100.

7. Swelling index: The swelling index of the microspheres were calculated by using the formula, Swelling index= (mass of swollen microspheres - the mass of dry microspheres/mass of dried microspheres) 100.

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 GIT. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

SUSTAINED DRUG DELIVERY

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents.

SITE-SPECIFIC DRUG DELIVERY SYSTEMS

The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug.

ABSORPTION ENHANCEMENT

Drugs which are having poor bioavailability because of site-specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

REDUCED FLUCTUATIONS IN DRUG CONCENTRATION

Continuous input of the drug following Controlled release Gastro-retentive dosage form (CRGRDF) administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration-dependent adverse effects that are associated with peak concentrations can be prevented.

Table 1: TYPES OF DOSAGE FORM[18]

Sr. No.	DOSAGE FORM	DRUGS
1	Microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Terfenadine, Tranilast.
2	Granules	Diclofenac sodium, Indomethacin, Prednisolone
3	Films	Cinnarizine
4	Powders	Several basic drugs
5	Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-Dopa, Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid.
6	Tablets/pills	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnarizine, Diltiazem, Fluorouracil,

Table 2: MARKETED PRODUCTS OF FDDS[18]

Sr. No.	BRAND NAME	DRUG (DOSE)	COMPANY, COUNTRY	REMARKS
1.	Modapar®	Levodopa(100 mg), Benserazide (25 mg)	Roche Products, USA	Floating CR capsule
2.	Valrelease®	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating capsule
3.	Liquid Gavison®	Al hydroxide (95 mg), Mg carbonate (358 mg)	GlaxoSmith Kline, India	Effervescent floating liquid alginate
4.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate
5.	Conviron	Ferrous sulfate	Ranbaxy, India	Colloidal gel forming FDDS
6.	Cifran OD®	Ciprofloxacin(1gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec®	Misoprostal(100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

CONCLUSION:

The development of Floating Microspheres can be advantageous for the administration of some important drugs and significantly improves their therapeutic outcome. Gastroretentivity of dosage form can be achieved by the development of devices that can float over the gastric fluids.

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