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FLOATING MICROSPHERES: A PROMISING NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Floating drug delivery system is one of the novel drug delivery system. Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without effecting gastric emptying rate for a prolonged period of time. The floating microspheres should be evaluated for micromeritic properties, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release of microspheres. The present review briefly addresses the physiology of the gastric emptying process with respect to the floating drug delivery system. 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 Microspheres/hollow microspheres/microballons are considered to be one of the most promising floating systems, because they combine the advantages of multiple unit systems, good floating properties and are prepared using assorted polymers. However, the success of these microspheres is limited owing to their short residence time at the site of absorption the floating microspheres have been developed in order to overcome frequent dosing to release the drug slowly in the GIT. These are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and target the drug to specific site at a predetermined rate. Floating microspheres are gastro retentive drug delivery systems based on non-effervescent approach. They are spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of protein or synthetic polymers with diameters 1µm to 1000µm. Microspheres are low density systems that have sufficient buoyancy to float over the gastric contents and remain in stomach for prolonged period

Floating drug delivery system: Floating drug delivery systems were first described by Davis in 1968. The gastric residence time of drugs is prolonged by using these systems. Several techniques are used to design gastro retentive dosage forms. These include 1.floating, swelling,

inflation, adhesion, high-density systems and low density systems that increase the gastric residence time. These systems floats over the gastic contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration. A minimal gastric content is 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 surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Gastric retention is useful for drugs which

a) Act locally
b) Have a narrow absorption window in the small intestinal region.
c) Unstable in the intestinal environment.

Types of FDDS: Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS:

d) A. Effervescent System and
e) B. Non- Effervescent System

Various dosage forms developed for gastric retention include,

a) Floating tablets
b) Floating beads
c) Pellets
d) Floating granules
e) Floating microspheres.

Polymers used in floating microspheres: floating microspheres can be prepared by using both hydrophilic and hydrophobic polymers.

- hydrophilic polymers
- hydrophobic polymers
- biodegradable polymer
- non-biodegradable hydrophobic polymers
- hydrogels
- soluble polymers

Advantages:

- Increase patient compliance.
- Bioavailability enhances.
- Gastro retention time is increased.
- Enhance absorption of drugs.
- Drug release in controlled manner for prolonged period
- Avoid gastric irritation.
- Better therapeutic effect of short half-life drugs can be achieved.
- No risk of dumping and released, drug uniformity compared to single unit floating drug delivery dosage systems.
- Site specific drug delivery to stomach can be achieved.

Disadvantages:

- Drugs that may irritate the stomach lining or as unstable in its acidic environment should not be formulated in gastro retentive systems.
- Drugs such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.

General method of preparation:

1. Single emulsion solvent evaporation technique.
2. Double emulsion solvent evaporation technique.
3. Coacervation phase separation technique.
4. Spray drying and spray coating.
5. Solvent extraction.
6. Polymerization technique.

a) Emulsion

b) Bulk

c) Suspension.

1. Single emulsion solvent evaporation 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.
EX: o/w (clonazepam) w/o(Timolol)

2. Double emulsion method:

Aqueous solution of polymer + drug
Dispersion in oil/organic phase,
Vigorous homogenization (sonication)
Primary emulsion - Addition of a aqueous solution of PVA.

⇓

W/o/w multiple emulsion addition of large aqueous phase.

⇓

Microspheres in solution. (Evaporation/centrifugation, washing, drying)

⇓

Microspheres

3. Coacervation phase separation technique: Aqueous/organic solution of polymer

⇓

Drug dispersed or dissolved in the polymer solution. It is a phase separation technique, salt addition, non solvent addition of incompatible polymer, etc.

⇓

Polymer rich globules.

⇓

Microspheres in aqueous/organic phase Separation/drying.

⇓

Microspheres

4. Spray drying and spray coating: Polymer dissolve in volatile organic solvent (acetone, dichloromethane)

⇓

Drug dispersed in polymer solution under high speed homogenization.

⇓

Atomized in a stream of hot air

⇓

Due to solvent evaporation small droplet or Fine mist form.

⇓

Leads to formation of microspheres

⇓

Microspheres separated from hot air by cyclone Separator, trace of solvent are removed by Vaccum drying.

Solvent Extraction:

Drug is dispersed in organic Solvent (water miscible organic Solvent such as isopropanol)

Organic phase is removed by extraction with water (this process decreasing hardening time for microspheres)

Hardening microspheres

Emulsion polymerization: Monomer and Aq. solution of NaoH, initiator, surfactant, and stabilizer are Dispersion with vigorous stirring

Micellar solution of polymer in aqueous medium. Polymerization

Microspheres formation, Centrifugation, washing, drying

Microspheres

BULK POLYMERIZATION: Monomer + bioactive material + initiator, Heated to initiate polymerization, Initiator accelerate rate of reaction.

Polymer(block)

Moulded/ fragmented

Microspheres

Suspension polymerization: Monomer + bioactive material + initiator are Dispersion in water and stabilizer

Droplet - vigorous, agitation and polymerization by heat

Separation & drying

Microspheres

Mechanism of Floating Microspheres: The polysaccharides and polymers used in the preparation of microspheres coming contact with the gastric fluids will hydrate to form colloidal gel barrier is formed when microspheres come in contact with gastric fluids this gel barriers controls the rate of fluid entry into the device and controls the drug release. The air trapped by the swollen polymers lowers the density angles buoyancy to the microspheres but there should be a minimum of the gastric fluidin order to allow the microspheres to float.

CHARACTERIZATION OF FLOATING MICROSPHERES:

Micromeritic properties:

Particle size: The particle size of the microspheres was measured using an optical microscopic method and mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micro meter.

Bulk densities: Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10 gm. sample of granules was placed into 25 ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and the bulk density was calculated using the equation (values expressed in gm/cm3) Bulk density= weight of sample/ Volume of sample

Tapped density: The tapping method can be used to calculate tapped densities. The volume of weighed quantity of microspheres was determined after 100 taps as well as 1000 taps using tapped density apparatus. Tapped density= weight of the sample/ Tapped volume

Compressibility Index and Hausner Ratio: Compressibility index and Hausner ratio was calculated from the values of bulk density and tapped density by using following formulas:

% Compressibility index= tapped density – bulk density/ tapped densityx100

Hausner's ratio = tapped density/bulk density

Angle of Repose: The angle of repose θ of the microspheres, which measures the resistance to particle flow, was calculated as per table.

Percentage yield: Percentage yield of floating microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula.

% yield = (actual weight of product/total weight of drug and Excipients) ×100

Drug entrapment efficiency (DEE): The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula:

DEE = (amount of drug actually present/theoretical drug load expected) × 100

Swelling studies: Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies may be determined by using dissolution apparatus, optical microscopy and other sophisticated techniques which include H1 NMR imaging, confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus was calculated as per the following formula.

Swelling ratio= weight of wet formulations/ Weight of formulations

Scanning Electron Microscopy (SEM): Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure.

***In-vitro* buoyancy:** Microspheres (300mg) were spread over the surface of USP XXIV dissolution. Apparatus type II filled with 900 ml of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

Buoyancy (%) = $W_f \times 100 / W_f + W_g$

***In-vitro* drug release studies:**

For such type of studies USP dissolution apparatus at particular speed is used.

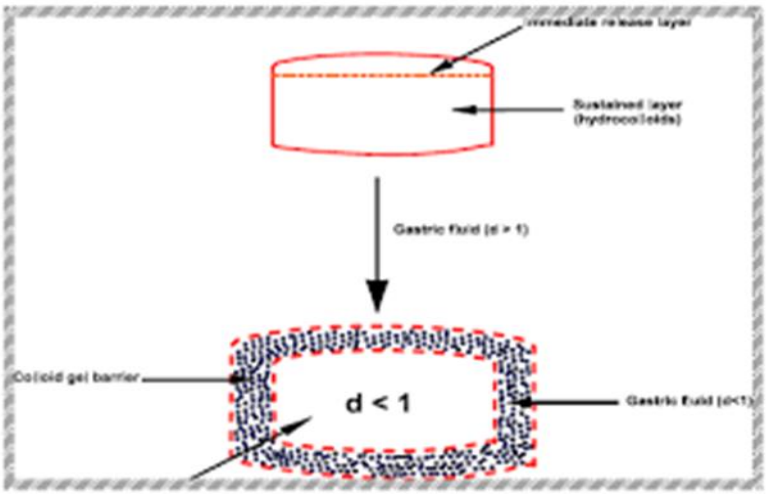


Fig: Intra gastric bilayer floating tablets.

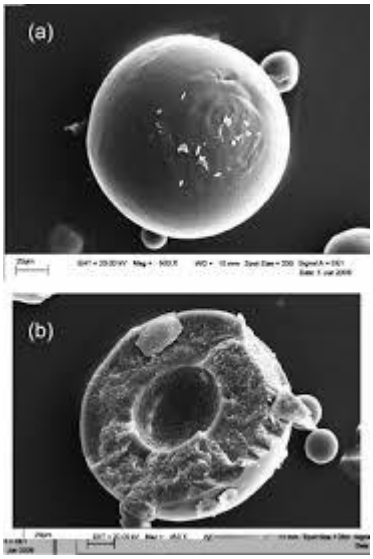


Figure-1: SEM photography of (a) outer surface of a microsphere

(b) Inner surface of a broken half of microsphere.

MATERIALS USED IN PREPARATION OF MICROSPHETRES:

- **POLYMERS:**

Eudragit	Cellulose acetate	Chitosan	carbopol
Acrycoat	Acrylic resin	methocil	agar
Polyacrylates	polycarbonates	PVA	PEO

- **CHANELLING AGENTS**:

HPMC	Citric acid	PVP	PEG

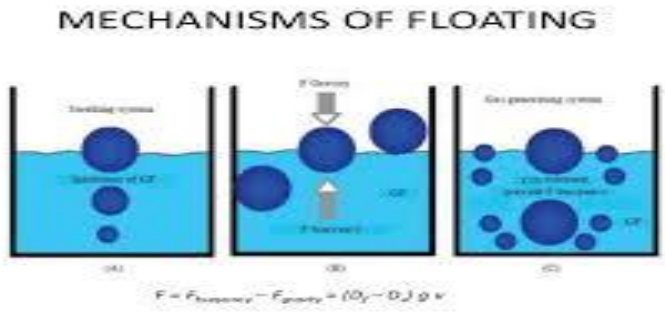
- **SOLVENTS:**

Acetone	Dichloromethane	Water
Chloroform	Ethyl cellulose	Ethanol
Isopropanol	Ethyl acetate	Acetone nitrile

EXAMPLES OF DRUGS INVOLVED IN FLOATING MICROSPHERES:

Drug	Catergory	Method of preparation	Uses	Brand name
Verampamil	Calcium channel blocker	Solvent diffusion evaporation method	Hypertension,angina	Calan, Isoptin
Acebutolol	Beta-blockers	Solvent diffusion evaporation method	hypertension	Sectra
Lafutidine	Anti-ulcer	Ionotropic gelation method	Gastric ulcer, deuodenalulcer, acutegastrities	Laciloc
Cimetidine	H2 blockers	Solvent evaporation method	Certain types of ulcers and also used to treat gastroesophagal reflex disease(GERT)	Cimetin
Cinnarizine	antihistaminic	Solvent evaporation	Calcium channel blockers	Cervaton
flupertinemeleate	Non-steroidal analgesic, non-opioid	Solvent evaporation method	Alzheimer's disease, multiple sclerosis	Fludol
Ranolazine	Anti-angina	Emulsion solvent diffusion evaporation	Chronic angina, blood pressure control	Rolazin
Ritonavir	Protease inhibitor	Ionic gelation tecnique	Used to treat HIV/AIDS	Norvir
Salbutamol sulphate	B2-adrenergic agonists	Solvent evaporation method	Asthma, chronic bronchitis, breathing disorders	Bronchilet
Famotidine	Histamine H_2-receptors antagonist	Solvent evaporation (oil in water emulsion)	Gastric ulcers, duodenal ulcer ,Zollinger' Ellison syndrome	Facid-20 Tab
Metformin hydrochloride	Anti-diabetic	Non-aqueous solvent evaporation	Type-2 diabetes	B form
Cephalexin	antibiotic	Emulsion solvent evaporation technique	Respiratory, urinary tract infection	cefF kid tab
Norfloxacin	antibiotic	Non aqueous solvent diffusion method	Gonorrhoea, urinary tract infections	normax tab
Captopril	ACE -inhibitor	Solvent evaporation	Hyper tension, congested heart failure	Catopil
Nateglinide	Anti diabetic	Oil in water emulsion solvent evaporation technique	Type-2 diabetes	Starlix

Flow	Angle of repose	Carr's index (%)
Excellent	<25	5 -15
Good	25 -30	12 -16
Fair to passable	30 -40	18 – 21
Poor	>40	23 – 35
Very poor		33 – 38
Extremely poor		>40



Distilled water and dissolution fluid is maintained at 37±10C. Samples withdrawn at periodical intervals and are analyzed spectrophotometrically. The volume was replenished with the same amount of fresh medium to maintain the sink condition.

APPLICATIONS:

- Used as carriers for drugs
  Eg: anti fungals, sulphonamides, antivirals,antibiotics.
- Effective in sparingly soluble and insoluble drugs
  Eg:griseofulvin,p-nitro aniline
- Microspheres of NSAIDS reduce gastric irritation
  Eg: aspirin , ibuprofen
- Used to treat gastritis, oesophagitis ,stomach & duodenal ulcers.
  Eg: terfenadine , tranilast.

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. Hollow microsphere 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.

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