EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 1
229-233
Year: 2021

A REVIEW ON FLOATING MICROSPHERE

Shubham Nawani* and Vijay Jyoti

Department of Pharmaceutical Sciences, H. N. B Garhwal University, Srinagar (Uttarakhand).

***Corresponding Author: Shubham Nawani**
Department of Pharmaceutical Sciences, H. N. B Garhwal University, Srinagar (Uttarakhand).
DOI: https://doi.org/10.17605/OSF.IO/45MYU

Article Received on 03/11/2020 **Article Revised on 23/11/2020** **Article Accepted on 13/12/2020**

ABSTRACT
The design of floating drug delivery Systems (FDDS) should be primarily aimed to achieve more predictable and increased bioavailability. Now-a-days most of the pharmaceutical scientist is involved in developing the ideal FDDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release tablet. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. This review paper presents formulation and characterization of floating microsphere.

KEYWORDS: Floating Microsphere, FDDS, GDDS.

INTRODUCTION
Floating microspheres are gastro retentive drug delivery systems based on a non-effervescent approach. Hollow microspheres, micro balloons or floating micro particles are terms used synonymously for floating microspheres. Floating microspheres are, in a strict sense, spherical empty particles without a core. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[1]

Gastrointestinal retention[2]
Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) For maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT. These are outlined and briefly discussed.

1. **Basic gastrointestinal tract physiology:** Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.
2. **Stomach physiology:** The stomach is an expanded section of the digestive tube between the esophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae. There are images to four major types of secretary epithelial cells that cover the surface of the stomach and extend down gastric pits and glands: Mucous cells: secrete alkaline mucus that protects the epithelium against shear stress and acid. Parietal cells: secrete hydrochloric acid. Chief cells: secrete pepsin, a proteolytic enzyme. G cells: secrete the hormone gastrin. The contraction of gastric smooth muscle serves two basic functions Ingested food is crushed, ground, mixed and liquefying to form Chyme. Chyme is forced through the pyloric canal into the

small intestine, a process called gastric emptying. Gastric motility: Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems. A large battery of hormones has been shown to influence gastric motility- for e.g. both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach. The bottom line is that the patterns of gastric motility likely are a result from smooth muscle cells integrating a large number of inhibitory and stimulatory signals. Liquid readily pass through the pylorus in spurts, but solids must be reduced to a diameter of less than 1-2 mm before passing pyloric gatekeeper.

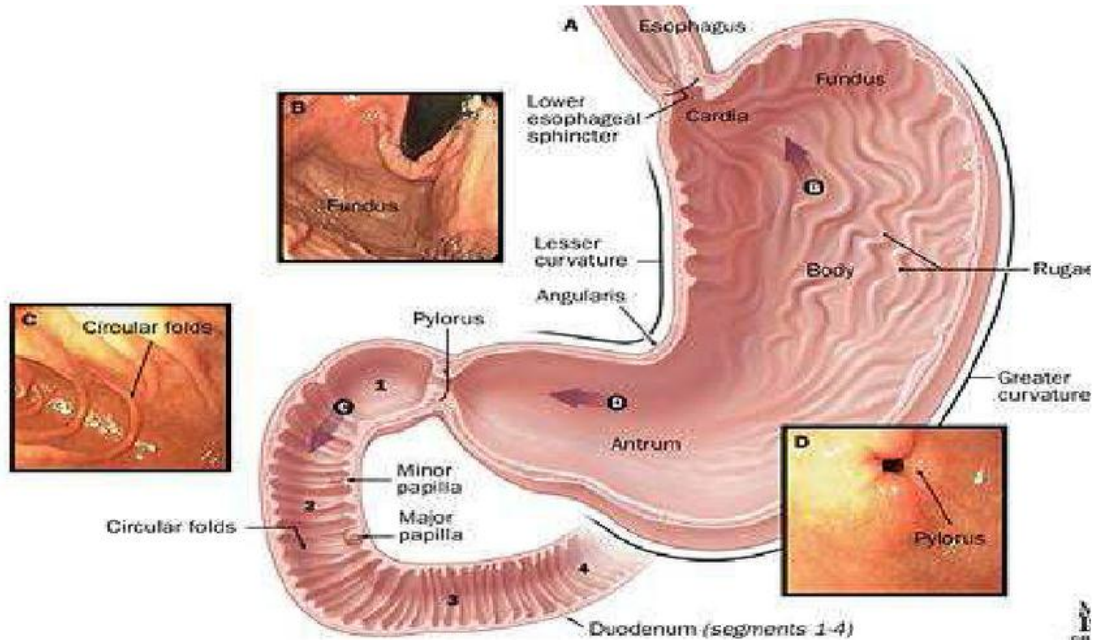

Fig. 1: Physiology of Stomach.

List of drugs explored for various floating dosage forms[2]

1. **Microspheres Tablets /Pills:** Chlorpheniramine maleate, Aspirin, griseofulvin, Acetaminophen, p-nitro aniline, Acetylsalicylic acid, Ibuprofen, Amoxicillin trihydrate, Terfenadine, Ampicillin, Trani-last, Atenolol, Theophylline, Captopril, Isosorbide di nitrate, Sotalol, Isosorbide mononitrate.
2. **Films:** P-Amino benzoic acid, Cinnarizine, Piretanide, Prednisolone, Quinidine gluconate.
3. **Granules:** Cinnarizine, Diclofenac sodium, Diltiazem, Indomethacin, Fluorouracil, Prednisolone, Isosorbide mono nitrate, Isosorbide di nitrate.
4. **Powders:** Riboflavin, phosphate, Sotalol, Theophylline.
5. **Capsules:** Verapamil HCl, Chlordiazepoxide HCl, Diazepam, Furosemide, L-,dopa and benserazide Misoprostol, Propranolol HCl, Ursodeoxycholic acid, Nicardipine .

Formulation of floating microsphere[3]

A. Effervescent systems

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, C02 is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

a. Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid (like ether, cyclopentane), that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and 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.

b. Gas-generating systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. How the dosage form float is shown in the figure 2.

B. Non-effervescent systems

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

a. Colloidal gel barrier systems

Hydro dynamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975.Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids.e.g.HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. 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 form.

b. 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 -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.

c. Hollow microspheres

Hollow microspheres (microballons), 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 of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.

d. Intragastric/Microporous compartment system

The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with walls of the stomach. Novel levodopa gastro retentive dosage form based on unfolding polymeric membranes which combines extended dimensions with high rigidity. It was folded into a large size gelatin capsules. In vitro studies showed that unfolded form reached within 15 minutes after administration and it was confirmed in vivo in beagle dogs. The unfolded form was maintained for at least 2 hours. It was concluded that this dosage form could improve therapy of different narrow absorption window drugs. However, there are possibilities of the polymeric films to get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries and repeated administration of rigid dosage form may result in gastric obstruction.

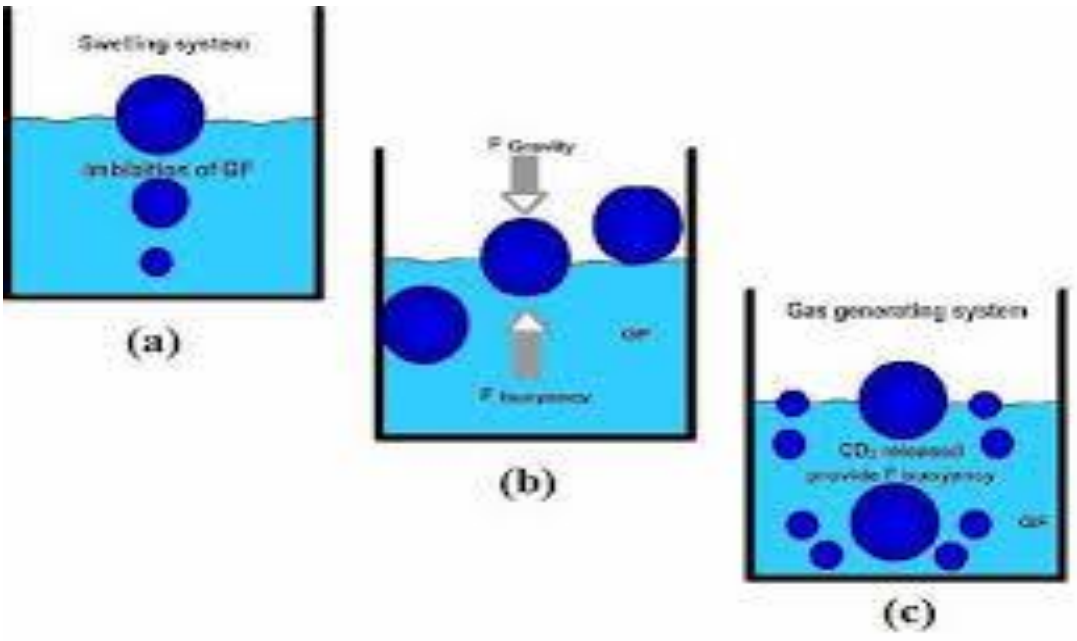

Fig. 2: Mechanism of floating of beads.

Evaluation of microspheres[4,5]

1. 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.

2. Bulk density

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10gm. 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

3. 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 sample/Tapped volume

4. 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 density X100

Hausner Ratio=Tapped density/Poured or Bulk density

5. 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

6. 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 0.1NHCl. 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

7. 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.

8. 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.

9. In-vitro buoyancy

Microspheres (300mg) were spread over the surface of a 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.

10. Floating behavior

The floating test on the microspheres is carried out using the dissolution method II apparatus, specified in the USP XXII. The microspheres are spread over the surface of the dispersing medium (900 ml), which is agitated by a paddle rotated at 100 rpm. Disintegration test solution No. 1 (pH 1.2), containing Tween 20 (0.02%, w/v), was used as a dispersing medium to simulate gastric fluid. After agitation for a previously determined interval, the hollow microspheres that floated over the surface of medium and those that settled to the bottom of the flask were recovered separately. After drying, each fraction of the hollow microspheres was weighed.

11. In vitro release studies

In vitro dissolution studies can be carried out in a USP paddle type dissolution assembly. Microspheres equivalent to the drug dose are added to 900 ml of the dissolution medium and stirred at 100 rpm at 37 ± 0.5 °C. Samples are withdrawn at a specified time interval and analyzed by any suitable analytical method, such as UV spectroscopy or HPLC, etc.

12. In vivo studies

In vivo studies are generally conducted in healthy male albino rabbits weighing 2-2.5 kg. The animals are fasted for 24 hours before the experiments; however, they are given free access to food and water during the experiments. Blood samples (2 mL) are collected from the marginal ear vein into heparinized centrifuge at an appropriate time interval has carried out an in vivo study in healthy human volunteers. The pharmacokinetic parameters were determined by the analysis of urinary excretion data.

Applications of floating microspheres[6]

1. Floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) are taken up only from very specific sites of the GI mucosa.
2. Hollow microspheres of non-steroidal anti-inflammatory drugs are very effective for controlled release, and reduce the major side effect of gastric

irritation. For example, floating microspheres of indomethacin are quite beneficial for rheumatic patients.

3. Floating microspheres are especially effective in the delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate, and thus transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid the risk of solubility becoming the rate-limiting step in release, by restricting such drugs to the stomach. Positioned gastric release is useful for drugs efficiently absorbed through the stomach, such as verapamil hydrochloride. The gastro retentive floating microspheres will beneficially alter the absorption profile of the active agent, thus enhancing its bioavailability.
4. Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating Helicobacter pylori from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and esophagitis.

CONCLUSION

Many drugs have been formulated as sustained release and polymer mediated effervescent and non-effervescent designed on the basis of delayed GIT emptying and buoyancy principles. So these dosage forms play the best role in the treatment of GIT diseases.

REFERENCE

1. http://www.pharmatips.in/Articles/Pharmaceutics/Tablet/Classification-Of-Floating-Tablets.aspx
2. Anupama S, Rathnaparkhi M P. Shilpa C, Floating Drug Delivery System: An Overview, International Journal of Research and Development in Pharmacy and Life Sciences, 2014; 3(5): 1106-1115.
3. Anamika S, Kalpesh G, Virender S, Rajneesh KS, Ashok D, Floating Microspheres as Drug Delivery System, American Journal of Pharmacy and Pharmaceutical Sciences, 2014; 1(2): 27-36.
4. Gayathridevi M, Adlin J N, Tamizh Mani T, Floating microsphere: A review, International Journal of research in pharmacy and chemistry, 2016; 6(3): 501-510.
5. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H, Physicochemical properties to determine the buoyancy of hollow microsphere(micro balloon) prepared by the emulsion solvent diffusion method, European Journal of Pharmacy and Biopharmaceutics, 2003; 55: 297-304.
6. Mukund J Y, Kantilal B R, Sudhakar R N, Floating microspheres: a review, Brazilian Journal of Pharmaceutical Sciences, 2012; 48(1): 17-30.