A Unique Dosage Form: Floating Microspheres: A Concise Review

Harnish Patel*1, Priyanka Patel2, Patel Chirag J3, Ramesh Dhani4

1Director, Research Scholar Hub, Gujarat.
2Managing Editor, IJPRBS, Gujarat.
3Dept. of Pharmaceutics, Maharishi Arvind Institute of Pharmacy, Mansarovar, Jaipur, Rajasthan, India
4Dept. of Pharmaceutical Chemistry, Ratnam Institute of Pharmacy, Nellore, A. P, India-524346

*E-mail: researchscholarhub@gmail.com
Available Online: 27 November 2013

ABSTRACT
Various approaches have been worked out to improve the retention of oral dosage form in the stomach like floating systems, swelling and expanding systems, bioadhesive systems, high density systems. Gastroretentive drug delivery system offers several advantages besides providing better bioavailability to poorly absorbed drugs and a required release profile thus attracting interest of pharmaceutical formulation scientists. Floating microspheres (Hollow Microspheres) are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core, free flowing powders consisting of proteins or synthetic polymers, ideally having a size in the range 1-1000 micrometer. Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose, scanning electron microscopy, in vitro floatability studies, in vivo floatability studies, in vitro drug release studies and stability studies etc.

Keywords: Floating Microspheres, Gastroretentive, Hollow Microspheres, Absorption

INTRODUCTION
Floating microspheres is one among the several approaches to gastroretention, like mucoadhesion, flotation, sedimentation, expansion, modified shape systems etc. These systems are useful in overriding the several problems encountered during the development of a pharmaceutical dosage forms. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Floating microspheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilise only in stomach, Gastric retention time is increased because of buoyancy. Floating microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core.

Appropriate Candidates for Floating Drug Delivery
Appropriate candidates for floating drug delivery system are the molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.
1. Drugs which are primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Scinnaarazine.
2. Drugs with narrow absorption window in GI tract, e.g., Para aminobenzoic acid, furosemide, riboflavin in a vitamin deficiency and Levodopa.
3. Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate.
4. Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
5. Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.

Methods of Preparation of Hollow Microspheres
Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. Polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the
temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties.

**List of Polymers Used:**
Chitosan, Eudragit, Cellulose acetate, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide, Polycarbonates, Polyethylene oxide and Acrylic resins.

**Mechanism of Drug Release from the Microspheres**
The mechanism of drug release from multiparticulates can occur in the following ways:
1. **Diffusion:** On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.
2. **Erosion:** Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.
3. **Osmosis:** In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

**Evaluation:**
1. **Yield of Microspheres**
The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres. % Yield = (Actual weight of product / Total weight of excipients and drug) x 100
2. **Particle size determination**
The particle size can be determined by using an optical microscope under regular polarized light, and the particle size was calculated by measuring 100 particles with the help of a calibrated coulometer.
3. **Bulk density**
Bulk density can be determined by three tap method, after filling the weighed quantity of microspheres in a graduated cylinder, the volume occupied by microspheres should be determined.
4. **Optical Microscopy**
This method was used to determine particle size by using optical microscope (Meizer OPTIK). The measurement was done under 450x (10x eye piece and 45x objective) and 100 particles were calculated.
5. **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.
6. **Entrapment Efficiency**
Microspheres containing of drug should be crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was filtered then assayed by UV-visible spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.
7. **Swelling Index**
This technique was used for characterization of sodium alginate microspheres were performed with swelling index technique. Different solution (100 mL) such as (distilled water, buffer solution of pH 1.2, 4.5, 7.4) were taken and alginate microspheres (100 mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37°C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.
8. **Floating Behavior**
Floating microspheres should be placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant microspheres was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.
Buoyancy (%) = Wf / Wf + Ws
Where, Wf and Ws are the weights of the floating and settled microparticles.
9. **In-Vitro Release Studies**
The release rate of floating microspheres was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at 37 ±1°C at a rotation speed of 100 rpm. Perfect sink conditions prevailed.
during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a 0.25 µm membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate. 

10. In-Vivo Studies
The in-vivo floating behavior can be investigated by X-ray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs. The in-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models.

Applications of Floating Microspheres
1. Floating microspheres are especially effective in 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 the 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 chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.

2. The 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.

3. Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quiet beneficial for rheumatic patients.

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5. The drugs recently reported to be entrapped in hollow microspheres include Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride and Riboflavin, Aspirin, Griseofulvin, Ibuprofen, Terfenadine.

6. 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 oesophagitis.

CONCLUSION
Multiparticulate drug delivery systems provide several all the advantages including greater flexibility and adaptability of microparticulate dosage forms which gives clinicians and those engaged in product development powerful new tools to optimize therapy. Floating microspheres are promises to be a potential approach for gastric retention enhances the bioavailability and controlled delivery of various therapeutic agents. Floating microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development.

REFERENCES