**MICROBALLOONS: AN EMERGING NOVEL DRUG DELIVERY TO IMPROVE GASTRORETENTION OF DRUGS**

Dr. Kanjarla Narasimha and Sravanthi Pulla*

Chaitanya Deemed to be University, Kishanpura, Hanamkonda, Telangana, India.

**ABSTRACT**

Hollow microballoons (microspheres) are spherical empty particles without core. Microballoons (Hollow microsphere) are a drug delivery system that promises to be a potential approach for gastric retention. Microballoons drug-delivery systems are based on a noneffervescent system containing empty particles of spherical shape without core ideally having a size less than 200 micrometers. Microballoons drug delivery systems have shown to be of better significance in controlling the release rate for drugs having site-specific absorption. The floating microballoons showed gastro retentive controlled release delivery with efficient means of enhancing the bioavailability and promises to be a potential approach for gastric retention. Optimized hollow microspheres will find the central place in novel drug delivery, particularly in safe, targeted and effective in-vivo delivery promises to be a potential approach for gastric retention. They are gastro retentive drug-delivery systems, which provide controlled release properties. The advantages, limitations, methods of preparation of hollow microsphere, applications, polymers used in hollow microspheres, characterizations of microballoons and formulation aspects with various evaluation techniques are covered in detail.

**KEYWORDS:** Microballons, Gastroretentive, Floating, Novel drug delivery system

**INTRODUCTION**

Oral administration of drug is most preferred type of route of drug administration\(^1\). Microballoons are gastro retentive drug-delivery systems with the noneffervescent approach. Microballoons (Hollow microsphere) are in a strict sense, empty particles of spherical shape
without a core. These microspheres are characteristically freeflowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 µm.\[^2\]

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. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Floating Drug Delivery Systems (FDDS) or hydrodynamically balanced systems are among the several approaches that have been developed in order to increase the gastric residence time of dosage forms. FDDS is useful for drugs acting locally in the proximal gastrointestinal tract and it has a bulk density lower than gastric fluids and thus remains buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and better control of fluctuations in plasma drug concentrations. The systems are also used for poorly soluble drugs or unstable in intestinal fluids.\[^3\]

Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.\[^4\]

Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit® S and cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio.\[^5\]

Hollow microspheres / microballoons loaded with the drug in their outer polymer shell are prepared by a novel method such as solvent evaporation or solvent diffusion/evaporation to
create a hollow inner core. The drug and an enteric acrylic polymer mixture is dissolved in ethanol/dichloromethane solution and it is poured into an agitated solution of Poly Vinyl Alcohol (PVA) that as thermally controlled at 40 ºC. After the formation of stable emulsion, the organic solvent is evaporated from the emulsion by increasing the temperature under pressure or by continuous stirring. The gas phase is generated in the droplet of the dispersed polymer by the evaporation of dichloromethane and thus formed the hollow internal cavity in the microsphere of the polymer with the drug. The micro balloon continuously floats over the surface of an acidic dissolution media containing surfactant for more than 12 h.[6]

Advantages of Floating Microballoons[7]
1. Improved patient compliance due to a reduction in the dosing frequency.
2. Improvement in bioavailability due to better drug utilization.
3. Reduction in the incidence or intensity of adverse effects due to avoidance of fluctuation in plasma drug concentration.
5. Hollow microspheres are used to decrease material density and Gastric retention time is increased because of buoyancy.
6. Enhanced absorption of drugs that solubilize only in the stomach.
7. Release of the drug in a controlled manner for a prolonged period.
8. Site-specific drug delivery to the stomach can be achieved.
9. Avoidance of gastric irritation, because of sustained-release effect

Limitation of Floating Microballoons[7]
1. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through the gut.
2. Differences in the release rate from one dose to another.
3. Controlled release formulations generally contain a higher drug load and thus, any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
4. Dosage forms of this kind should not be crushed or chewed.

Formulation development Drugs
1. Drugs: Drugs with narrow absorption window in GI tract, primarily absorbed from stomach and upper part of GIT, locally act in the stomach, degrade in the colon, disturb normal colonic bacteria. E.g. aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin, para aminobenzoic acid, furosemide, calcium supplements, chlordiazepoxide &
scinnarazine riboflavin, levodopa, antacids and misoprostol, Ranitidine and metronidazole, amoxicillin trihydrate.

2. Polymers: Cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene oxide.

3. Solvents: It should have good volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres. e.g. ethanol, dichloromethane, acetonitrile, acetone, isopropyl alcohol, dimethylformamide.

4. Processing medium: It is used to harden the drug polymer emulsified droplets when the drug-polymer solution is poured into it, should not interact with the former; mainly used are liquid paraffin, polyvinyl alcohol and water.

5. Surfactant: They are stabilizers or emulsifiers; play the role of hardening the microspheres as well e.g. tween 80, span 80 and sodium lauryl sulphate.

6. Cross linking agent: Chemical cross-linking of microspheres can be achieved using cross linking agents such as formaldehyde, glutaraldehyde or by using diacid chlorides such as terephthaloyl chloride. The method is limited to drugs that do not have any chemical interaction with the cross-linking agent.

7. Hardening agent: This helps to harden the microspheres formed in the processing medium. e.g. n-hexane, petroleum ether (in case the processing medium is liquid paraffin)

Methods of Preparation of Microballoons

1. Solvent Evaporation Method:
2. Emulsion Solvent Diffusion Method:
3. Solvent Diffusion-Evaporation Technique:
4. Spray Drying:

1. Solvent Evaporation Method

In this method, a 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 suitable additive (surfactants/polymer) 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 oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers for the development of
such systems include Eudragit, HPMC K4M and ethyl cellulose etc. Polymers are mixed with drugs and further this mixture is dissolved in the solution of ethanol, acetone or dichloromethane either alone or in combination to get homogenous polymer solution. The resulting solution is poured into 100 mL of liquid paraffin rotating at 1500 rpm. The emulsion is formed and heated at 35 ºC temperature for 3hr. After the formation of a stable emulsion, the acetone or dichloromethane is completely evaporated and resulting solidified microballoons are filtered using Whatman filter paper. This hollow microballoons imparts the floating and sustained properties.[8]

![Fig. 1: Solvent Evaporation Method.](image)

2. Emulsion Solvent Diffusion Method: In the solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and an aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuses gradually out of the emulsion droplets into the surrounding aqueous phase and the aqueous phase diffuse into the droplets by which drug crystallizes. The mixture of drug-polymer is dissolved in the solution of ethanol: dichloromethane and this mixture are adding dropwise to polyvinyl alcohol solution. This solution is stirred at 1500 rpm for 1 h and at different temperature ranges. By changing the polymer concentration in the co-solvent and the ratio of ethanol to dichloromethane, it is possible to prepare microballoons with various drug contents.[9]
3. **Solvent Diffusion-Evaporation Technique**: This technique is with a slight modification of both the emulsion solvent evaporation method and the emulsion solvent diffusion method. Drugs, polymers and 0.1% of a surfactant such as PEG are mixed in the solution of ethanol: dichloromethane (1:1) at room temperature. This solution is slowly introduced into 80 ml of 0.46% w/w of polyvinyl alcohol as an emulsifier. This is stirred using propeller agitator for 1 h for evaporation of organic solvents and then filtered it.\([10]\)

4. **Spray Drying**: Spray drying is the most widely employed industrial process for particle formation and drying. It is an ideal process where the required particle size distribution, bulk density and particle shape can be obtained in a single step. First of all, polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. to form a slurry. The slurry is then sprayed into the drying chamber, concentration gradient of the solute forms inside the small droplet with the highest concentration being at the droplet surface. This is
because the time of the solute diffusion is longer than that of the solvent in the droplets evaporating during the drying process. Subsequently, a solid shell appears leading toward formation of microspheres. Separation of the solid products from the gases is usually accomplished by means of a cyclone separator while the traces of solvent are removed by vacuum drying and the products are saved for later use.\textsuperscript{[11]}

![Spray Drying method.](image)

**Characterization and Evaluation parameters for hollow Microballoons**

1. **Percentage Yield:** The percentage yield of the hollow microspheres is determined for drug and is calculated using the following equation.
   
   \[ \text{Yield} = \frac{M}{M_0} \times 100 \]
   
   Where \( M \) = weight of beads \( M_0 \) = total expected weight of drug and polymer.

2. **Micromeritic Properties:** Microballoons are evaluated by their micrometric properties such as particle shape and size, bulk density, tapped density, Hausner’s ratio and flow properties which are determined by Carr’s index, porosity and angle of repose.

3. **Compatibility Studies:** Infrared spectrum of the drug, drug-loaded microballoons, blank microballoons, physical mixture and empty microballoons are recorded using FTIR.\textsuperscript{[12]}

4. **In-vitro Buoyancy:** Appropriate quantity of hollow/empty microspheres are placed in 900 ml of 0.1N HCl. The mixture is stirred at 100 rpm for 8-10 h in the dissolution apparatus. After 8 to 10 h, the layers of buoyant microspheres are pipetted and separated by filtration particle which lies in the layer of sinking particulate are separated by filtration. Particles of both types (buoyant microspheres and settled microspheres) are dried in a desiccator until a constant weight is achieved.\textsuperscript{[13]}
Both the fractions of empty/hollow microspheres are weighed and in-vitro buoyancy is determined by the weight ratio of floating microspheres to the sum of floating and sinking microspheres.

\[ \text{Buoyancy (\%)} = \left( \frac{W_f}{W_f + W_s} \right) \times 100 \]

Where \( W_f \) and \( W_s \) are the weights of the floating and settled microspheres.

5. Scanning Electron Microscopy: Dry hollow microspheres are placed on an electron microscope brass stub a coated with gold in an ion sputter. Then pictures of microsphere are taken by Spectro random scanning of the stub. The microspheres are viewed at an accelerating voltage of 20KV. Scanning electron microscopy was performed to characterize the surface of formed microspheres. The samples for SEM were prepared by lightly sprinkling the microballoons on a double-adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300 Å under argon atmosphere using a gold sputter module in a high-vacuum evaporator. The samples were then randomly scanned using a Scanning Electron Microscope and photomicrographs were captured.\[14\]

6. In-vitro Drug Release Studies: The release rate of hollow microspheres is determined in a United States Pharmacopoeia (USP) basket type dissolution apparatus. A weighted amount of floating microballoons equivalent to 75 mg of the drug is placed in screening medium having smaller mesh size than the microballoons. The mesh is then tied with a nylon thread to avoid the escape of any microballoons and a glass bead used in the mesh to induce the sinking of microballoons in the dissolution medium. The dissolution test was performed in 900 mL medium at 100 rpm; at specified time intervals, aliquots are to be withdrawn, filter, dilute with the same medium and assay using a UV double-beam spectrophotometer.\[15\]

7. Data Analysis of Release Studies: Five kinetic models including the zero-order (cumulative percentage of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi matrix (cumulative percentage of drug release versus square root of time), Peppas Korsmeyer (log cumulative percent drug release versus log of time) and Hixon-Crowell release equations are applied to process the in-vitro release data.\[16\]

8. Swelling Studies:\[17\] Swelling studies are performed to calculate molecular parameters of swollen polymers. Swelling studies are determined by using dissolution apparatus, optical microscopy and other sophisticated techniques, which include H1NMR imaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI), etc.

The swelling studies by using Dissolution apparatus (USP dissolution apparatus USP-24) lab India disso 2000) is calculated as per the following formula.
Swelling ratio = Weight of wet formulation / Weight of formulation

9. In-vivo Studies: The in-vivo studies are performed on suitable animal models example such as a rat, beagle dogs, etc. The floating behavior can be investigated by radiographical studies using barium sulphate microballoons.\[18\]

10. Entrapment Efficiency: Microballoons containing drug equivalent to 100 mg are digested in a 10 mL mixture of dichloromethane and methanol (1:1 v/v). The mixture is to be placed in the centrifuge at 3000 rpm for 3 min and 1 ml of supernatant is then withdrawn and after suitable dilution, with distilled water, it is assayed spectrophotometrically. The percentage drug entrapment is calculated from the equation given below.

Entrapment Efficiency = Amount of drug actually present × 100 / Theoretical drug load expected.

Applications of Floating Microballoons:\[19\] Microballoons/hollow microspheres generally vary in density and therefore, used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications like.

1. Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa.
2. It provides sustained drug release behavior and releases the drug over a prolonged period of time. They are mainly fabricated as a floating controlled drug delivery system.
3. They can greatly improve the pharmacotherapy of the stomach through local drug release. Thus, eradicating Helicobacter pylori from sub-mucosal tissue of the stomach is useful in the treatment of peptic ulcers, chronic gastritis, gastroesophageal reflux diseases etc. Floating bio-adhesive microspheres of acetohydroxamic acid are formulated for the treatment of Helicobacter pylori infection. Hollow microspheres of Ranitidine HCl are also developed for the treatment of gastric ulcers.
4. 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 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 the chance for solubility to become the rate-limiting step in a release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through the stomach. The gastro-retentive floating microspheres
will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.

5. The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example, antiviral, antifungal and antibiotic agents are taken up only from very specific sites of the GI mucosa.

6. Hollow microspheres of non-steroidal antiinflammatory 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.

CONCLUSION
In the present review, we have briefed the potential of Microballoon in the gastro retentive drug delivery system. Due to low-density, sufficient buoyancy to float over-gastric contents and remain in the stomach for prolonged period microballoon are of practical importance in the gastro retentive drug delivery system. From the pharmaceutical aspect, further developments and research is needed to achieve better product quality by formulating floating microballoons. Floating micro-balloons have the advantage that they remain buoyant and distributed uniformly over the gastric fluid to avoid the variations of gastric emptying and release the drug for prolonged periods of time. The micro-balloons are characteristically freeflowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometers. The micro-balloons are prepared by solvent diffusion and evaporation methods to create the hollow inner core. The micro-balloons can be evaluated for surface morphology, flow properties, buoyancy, yield, percent drug loading, in-vitro release, stability at gastric pH and FT-IR studies. The floating micro-balloons are promising candidates for the development of a gastro retentive drug delivery system for potential therapeutic use.

REFERENCES
