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A review of microballoons: An advance technique for Gastroretentive drug delivery system

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Abstract
The purpose of writing this review on micro balloons is to accumulate the recent literature with a special focus on the novel technological advancements in floating drug delivery system to achieve gastric retention. Micro balloons (Hollow microsphere) promises to be a potential approach for gastric retention. Micro balloons drug-delivery systems are based on non-effervescent system containing empty particles of spherical shape without core ideally having a size less than 200 micrometer. Micro balloons drug delivery systems have shown to be of better significance in controlling release rate for drugs having site specific absorption. They are gastro retentive drug-delivery systems, which provide controlled release properties. The advantages, limitation, methods of preparation of hollow microsphere, applications, polymers used in hollow microspheres, characterizations of micro balloons and formulation aspects with various evaluation techniques and marketed products are covered in detail.

Keywords: Micro balloons, Gastro retentive, gastric time, gastric emptying, buoyancy

1. Introduction
Conventional oral dosage forms such as tablets, capsules provide a specific drug concentration in systemic circulation which do not release at the constant rate for prolonged period of time. Controlled release drug delivery system (CRDDS) provides drug release at a precontrolled, predictable rate either systematically or locally for intended duration of time and optimizes the therapeutic effect of a drug by controlling its release into the body with lower and less frequent dosing1

1.1 Gastro retentive drug delivery systems (GRDDS)
Dosage forms that can be retained in stomach for longer periods of time are called gastro retentive drug delivery systems (GRDDS).
GRDDS are suitable and beneficial for such drugs by improving their absolute bioavailability, therapeutics efficiency, increase gastric residence time (GRT), possible reduction of the dose, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment.

1.2. Floating drug delivery system
Many floating systems have been generated based on granules, powders, capsules, tablets, laminated films, beads and hollow microspheres [4, 5].
It can be classified into two systems: [6, 7]

1.2.1 Effervescent System
Volatile liquid containing systems (Intragastric floating GRDDS)
Gas-generating Systems (Intra gastric single layer and bilayered floating tablets, Multiple unit type floating pills)

1.2.2 Non-Effervescent Systems
Hydro colloidal gel barrier systems
Micro porous compartment system
Alginate and pectin beads
Hollow microsphere (Microballoons)

2. Micro balloons
Micro balloons are gastro retentive drug-delivery systems with non-effervescent approach. Micro balloons (Hollow microsphere) are in strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometer [8].
Micro balloons are considered as one of the most favorable buoyant systems with the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The slow release of drug at desired rate and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polylactic acid, Eudragit®S and hydroxy propyl methyl cellulose cellulose acetate are used in the formulation of hollow microspheres, and the release of drug can be modulated by optimizing polymer concentration and the polymer -plasticizer ratio [9].
Hollow microspheres / microballoons loaded with drug in their outer polymer shell are prepared by a novel methods 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 [10]. The gas phase is generated in the droplet of dispersed polymer by the evaporation of dichloromethane and thus formed the hollow internal cavity in the microsphere of the polymer with drug. The micro balloon is continuously float over the surface of an acidic dissolution media containing surfactant for more than 12 hours [11, 12].

3. Mechanism of drug release

Microballoons come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Microballoons of acrylic resins, Eudragits, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments [7].

4. Materials for preparation of microballoons

4.1 Drugs

Drugs with narrow therapeutic window in GI tract, mainly 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 amino benzoic acid, Furosemide, Calcium supplements, Chlordiazepoxide, Scinnarazine, Riboflavin, Levodopa, Antacids, Misoprostol, Ranitidine HCl, Metronidazole and Amoxicillin trihydrate.

4.2 Polymers

Cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene11, 15, 16

4.3 Solvents

It should have good volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres eg ethanol, dichloromethane (DCM), acetonitrile, acetone, isopropyl alcohol (IPA),dimethylformamide (DMF) [17].

4.4 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 processing medium are liquid paraffin, polyvinyl alcohol and water.

4.5 Surfactant

They are stabilizers or emulsifiers, play the role of hardening the microspheres as well. E.g. tween 80, span 80 and SLS.

4.6 Cross linking agent

Chemical cross-linking of microspheres can be achieved using cross linking agents such as formaldehyde, glutaraldehyde or by using di acid chlorides such as terephthaloyl chloride. The method is limited to drugs that do not have any chemical interaction with the cross-linking agent18.

4.7 Hardening agent

This helps to harden the microspheres formed in the processing medium eg n-hexane, petroleum ether (in case the processing medium is liquid paraffin) 19.

5. Method of preparation

5.1 Solvent evaporation method

The polymers for the development of such systems include Eudragit, HPMC KM4 and ethyl cellulose etc. Polymers are mixed with drug 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 35oC temperature for 3hr. After the formation of a stable emulsion, the acetone or dichloromethane is completely evaporated and resulting solidified microspheres is filtered using whattman filter paper. This hollow microspheres imparts the floating and sustained properties20

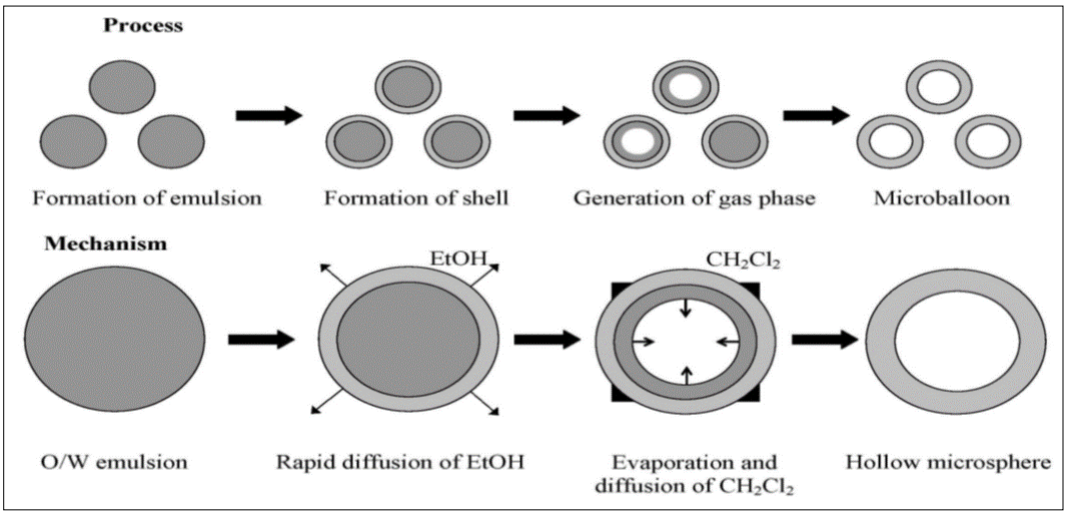

Fig 1: Solvent evaporation method

5.2 Emulsion solvent diffusion method

The mixture of drug polymer is dissolved in the solution of ethanol: dichloromethane and this mixture is adding drop wise to polyvinyl alcohol solution. This solution is stirred at 1500 rpm for 1 hour and at different temperature ranges21.

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and 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 diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse into the droplets by which drug crystallizes19,20 (Fig 2).

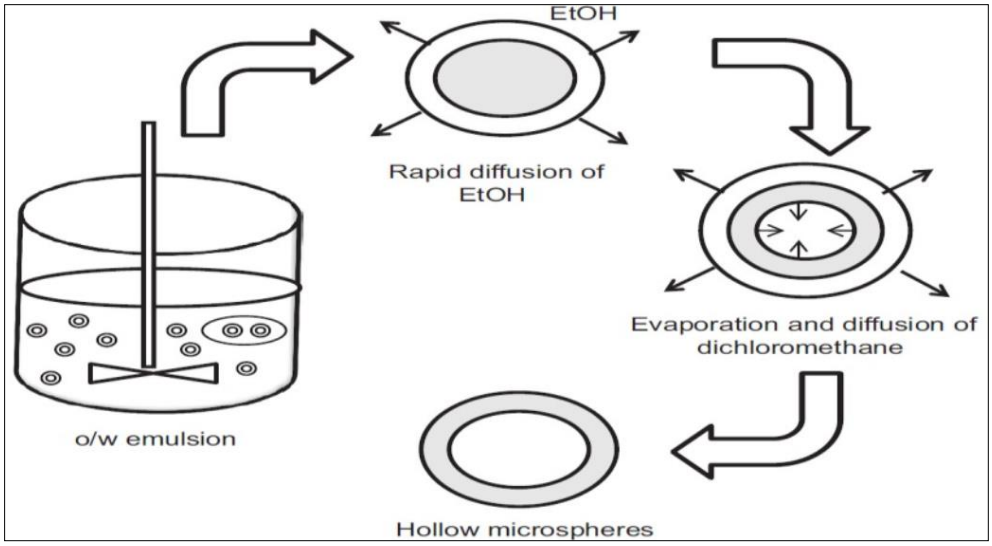

Fig 2: Emulsion solvent diffusion method

5.3 Solvent diffusion-evaporation technique

This technique is with slight modification of both emulsion solvent evaporation method and emulsion solvent diffusion method. Drug, polymers and 0.1% of 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 emulsifier. This is stirrer using propeller agitator for 1 hour for evaporation of organic solution and then filtered it22.

The best formulation is selected on the basis of optimized result of various process variables such as polymer ratio, drug: polymer ratio, stirring speed and concentration of emulsifier22.

5.4 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 step23. 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 use24 (Fig 3)

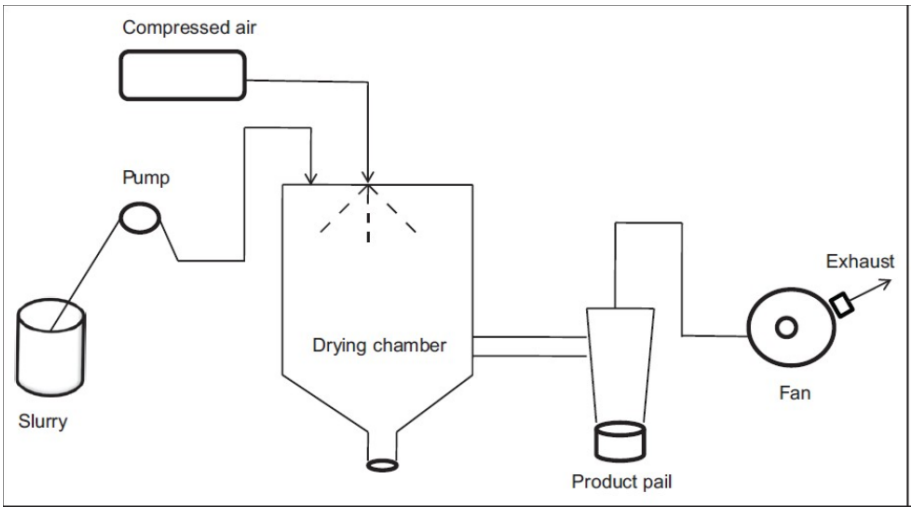

Fig 3: Spray drying method.

6. Evaluation of hollow microspheres

6.1 Percentage Yield

The percentage yield of the hollow microspheres is determined for drug and is calculated using the following equation34, 35, 36.

Yield=M/Mo x 100

Where M = weight of beads

Mo = total expected weight of drug and polymer.

6.2 Micromeritic properties

Micro balloons are evaluated by their micrometric properties such as particle shape and size, bulk density, tapped density, Hausner's ratio and flow properties which is determined by carr's index and angle of repose37. Particle size is determined by an optical microscopy, and average diameter of particle is calculated with the help of calibrated ocular micrometer (by measuring 200 to 300 particles) 38. True density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method. The hollow nature of microspheres is confirmed by scanning electron microscopy.

The compressibility/carr's index was calculated using following formula:

$$I = Vb - Vt / Vb \times 100$$

Where, Vb is the bulk volume and Vt is the tapped volume. The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability. True density is determined using a Helium densitometer. Porosity (e) is calculated using the following equation:

$$e = \{1- (\text{tapped density/true density})\} \times 100$$

Angle of repose of the micro balloons are determined by the fixed funnel method.

6.3 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 hours in dissolution apparatus. After 8 to 10 hours, the layers of buoyant microspheres are pipetted and separated by filtration. Particles 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 constant weight is achieved. 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 microspheres39.

$$\text{Buoyancy (\%)} = \{Wf / (Wf + Ws)\} \times 100$$

Where, Wf and Ws are the weights of the floating and settled microspheres

6.4 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 20KV40.

6.5 In-vitro drug release studies

The release rate of hollow microspheres are determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus.

A weighed amount of hollow microspheres (filled into a hard gelatin capsule) equivalent to dose of drug and place in the basket of dissolution rate apparatus containing dissolution medium. The dissolution fluid is maintained at 37 ± 1 °C and rotation speed at a specific rpm. Perfect sink conditions carry out during the drug release study. Few ml (5 ml) of samples are withdrawn at each time interval and analyzes using Liquid chromatography / Mass spectroscopy method to determine the concentration of microballoons present in the dissolution medium. The initial volume of the dissolution fluid is maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments are run in triplicate41.

6.6 Data analysis of release studies

Five kinetic models including the zero order (Equation 1), first order (Equation 2), Higuchi matrix (Equation 3), Peppas- Korsmeyer (Equation 4) and Hixon-Crowell (Equation 5) release equations are applied to process the in vitro release data to find the equation with the best fit using PCP Disso v3 software.

6.7 Swelling studies

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 formulations

6.8 In-vivo studies

The in-vivo studies are performed on suitable animal models example such as rat, beagle dogs etc. The floating behavior can be investigated by radio graphical studies using barium sulphate micro balloons.

7. Limitations

Some of the disadvantages were found to be as follows.

1. The modified release from the formulations.
2. 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 [19-20].
3. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut [21].
4. Dosage forms of this kind should not be crushed or chewed.
5. Differences in the release rate from one to another [22].

8. Applications

Various applications of micro balloons are given below

1. Micro balloons 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.
2. Floating microspheres can greatly improve the pharmacotherapy of stomach through local drug

release. Thus, eradicating Helicobacter pylori from sub-mucosal tissue of the stomach are useful in the treatment of peptic ulcers, chronic gastritis, gastro esophageal reflux diseases etc. Floating bio adhesive microspheres of aceto hydroxamic acid are formulated for treatment of Helicobacter pylori infection. Hollow microspheres of ranitidine HCl are also developed for the treatment of gastric ulcer [23].

3. Solid and Microballoons vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are.
4. 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.
5. These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres of tranilast are fabricated as a floating controlled drug delivery system. [24]
6. 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, Amino glycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa.
7. Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone. Floating hollow microcapsules of melatonin showed gastro retentive controlled-release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 hours e.g., Metoclopramide and Glipizide loaded Chitosan microspheres [25].
8. Micro balloons 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 [25].

9. Conclusion

The purpose of this review on microballoons is to accumulate the recent literature with focus on the development of formulations and applications. From the review we concluded that the micro balloons showed gastro retentive controlled release drug delivery and proved as the most promising drug delivery than conventional drug delivery system.

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