MICROBALOONS: An Incredible Gastro Retentive Drug Delivery System
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Abstract:
The purpose of writing this review on microballoons is to accumulate the recent literature with a special focus on the novel technological advancements in floating drug delivery system to achieve gastric retention. Microballoons (Hollow microsphere) promises to be a potential approach for gastric retention. Microballoons 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. Microballoons drug delivery systems have shown to be of better significance in controlling release rate for drugs having site specific absorption. The floating microballoons showed gastroretentive 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 gastroretentive 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 microballoons and formulation aspects with various evaluation techniques and marketed products are covered in detail.

Introduction:
The purpose of any drug delivery system is to provide the therapeutic amount of drug in the appropriate area of the body to achieve immediately and maintain the desired drug concentration. The simplest and most commonly used route for drug delivery has historically been oral ingestion. Drugs that are easily absorbed into the GIT and have a short life span are quickly removed from the bloodstream.

To avoid these problems oral controlled drug delivery systems have been developed as they gradually release the drug into the GIT and maintain a constant concentration of the drug in the serum. As the number and chemical variations of drugs increase, new strategies are needed to improve oral treatment. Therefore, the gastroretentive drug delivery system, which prolongs the duration of medication in the abdomen and improve their bioavailability, has been improved.

1.1. Gastro-retentive drug delivery system:
One of the most possible ways to achieve a long-term and predictable drug delivery profile in the intestinal tract is to control the duration of stay in the stomach i.e., the Gastro-retentive dosage form. These are mainly drug-controlled, long-lasting and time-consuming drug delivery systems. Therefore, the control of the placement of the drug delivery system in a particular region of the GI tract provides many benefits especially drugs that reflect the GI tract absorption window. To protect the hollow microspheres, floating drug delivery systems are being developed.

1.1.1. Floating drug delivery system (FDDS):
Floating Drug Delivery Systems (FDDS) have a much lower volume than stomach fluid and stay buoyant on the stomach for a long time, without affecting the rate of gastric emptying. The FDDS were further classified in to different types as shown in Fig 1.
1.1.2. Hollow microsphere/Microballoons:

Hollow microspheres are spherical empty particles without core and can remain in the stomach region for a long time. Hollow microspheres are gastro retentive drug delivery systems in the gut based on a non-effervescent process. Empty micro-spheres, small balloons, or a floating microparticle are used similarly for floating microparticles. Floating microspheres are spherical empty particles without a core. These are free-flowing particles with sizes ranging from 1 to 1000 mm. Empty microspheres / small balloons loaded with drugs on one of their polymer shelves are prepared with solvent evaporation / solvent dispersion/evaporation to increase the final time in the stomach of the dosage form. Commonly used polymers are polycarbonate, Cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin, etc… buoyancy and drug release Dependent on the dosage form or the quality of the polymer, the plasticizer used, polymer ratio, and solvent formulation. The micro balloons floated continuously over the surface of an acidic dissolution media containing for >12 hr. Currently, hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multi-unit systems and good floating. These microspheres are free-flowing low-density Powders less than 200 mm in size, consisting of proteins or synthetic polymers. continuous release of the drug from the buccal system improves gastric retention and reduces plasma drug concentration fluctuations. Several researchers have worked on Hollow microspheres. Francisco Marquez et al., developed a monodisperse made of hollow magnetite microspheres in a one-step process using a template-free hydrothermal method. YuningHuo et al., developed blank CdS-TiO2 microspheres with a brightly coloured photocatalytic function Kazuhiro S et al., Used calcite microspheres as a precursor to improving the formation of carbonated apatite carbonate microspheres as bone-replacement material. Changchun Wang et al., developed a uniform double-shell hollow microsphere blank from the new polymer spinal transformation method as an active acoustic echo imaging agent Kapil Kumar and AK Rai have opened new doors for the production of sterile hollow microspheres such as curcumin as drug delivery systems.

2. Method of preparation of hollow microsphere:

The empty microsphere can be adapted using any process discussed in most techniques but the choice of method largely depends on the type of polymer used, the intended use, and the duration of treatment. This is mainly enhanced by the preparation and its choice is determined equally by the formulation and dosage of the prepared drugs. In general, the methods of preparation are as follows:

A. solvent evaporation method
B. Emulsion solvent diffusion method
C. Single emulsion Technique
D. Double emulsion technique
E. Polymerization technique
F. Spray drying and congealing.

A. Solvent evaporation method:
This technique is widely used to obtain the controlled released drugs. In this method, the drug and polymer are mixed in an organic phase and dispersed in more amount of aqueous continuous phase, and stir it for some time to form an emulsion. by solvent evaporation technique different methods are used to prepare a hollow microsphere that depends on the hydrophilicity and hydrophobicity of drugs. for poorly water-soluble drugs the oil-in-water type method is merely used, whereas, for hydrophilic drugs, this method is not suitable because of dissolution and more loss of drug. W/o/w double emulsion method, o/w co-solvent method, and O/o non-aqueous solvent evaporation method can be used for incorporation of water-soluble drugs. Solvent evaporation is an easy way to make hollow microspheres where the process can be controlled easily and built-in microspheres show good product yield and high encapsulation efficiency. The schematic representation of solvent evaporation method is shown in Fig 2.

![Schematic representation of solvent evaporation method](image)

Fig 2: Schematic representation of solvent evaporation method
B. Emulsion solvent diffusion method:
Kawashima et al. proposed empty microspheres (so-called "micro balloons") that have been developed to increase the novel emulsion solvent diffusion method based on enteric acrylic polymeric containing a drug in the polymeric shell. Typically, this method involves the dispersion of a polymer solution with drugs in the dichloromethane and ethanol component into a wet solution of surfactants. Ethanol rapidly separates the outer layer of water and the polymer absorbs the droplets of dichloromethane. Subsequent rapid evaporation of dichloromethane leads to the formation of internal cavities within microspheres. The major advantage of the emulsion solvent diffusion method includes distribution of the same size and minimum hollow microspheres constructed and efficient process. However, a complex process cannot be easily controlled. The schematic representation of emulsion solvent diffusion method is showed in Fig 3.

Fig 3: Schematic representation of emulsion solvent diffusion method

C. Single emulsion technique:
In this process the microparticulate carrier of the natural polymer, which means that proteins and carbohydrates are prepared. Natural polymers are dissolved or dispersed in an aqueous medium followed by dispersing in an nonaqueous medium, ex. oil this second step in preparation for connecting the scattered Globule I is performed. Cross-linking can be obtained by heating or using a chemical cross-linker such as glutaraldehyde, formaldehyde butanol, diacid chloride, etc. After that in the organic phase, microspheres are formed which is then centrifuged, filtered, washed & dried. The single emulsion technique was depicted in Fig 4.
D. **Double emulsion technique:**
This method involves the formation of multiple emulsion duplicates of the type w / o / w. It is suitable for taking soluble drugs, peptides, proteins, and vaccines. Both natural and synthetic polymers are used for microsphere preparation. The aqueous protein & drug solution is dispersed by the lipophilic organic continuous phase. The continuous phase is usually composed of a polymer solution that ends up incorporating the proteins contained in the dispersed liquid phase. The main emulsion is placed under homogenization or sonication Prior to the aqueous solution of polyvinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then removed from the solvent application either by evaporation of the solvent by the solvent extraction process. The solvent evaporation is formed by keeping the emulsion in reduced pressure Stimulates the emulsion so that the organic phase evaporated out. An emulsion is added to a large amount of water in the organic phase that spreads out. The microsphere is formed, filter, and wash it with n-hexane, acetone, or other organic solvents to remove oil from the surface. The schematic representation of double emulsion technique was shown in Fig 5.
Fig 5: Double emulsion technique

**E. Polymerization technique:**
Polymerization techniques are commonly used to prepare highly differentiated microspheres, categorized into following types:

I. Normal polymerization.
II. Interfacial polymerization.

These techniques are carried out in liquid phase-

I. **Normal polymerization:**
   It is done using a variety of techniques such as mass, suspension, precipitation, emulsion, and micellar polymerization processes. In general, a monomer or a mixture of monomers and an initiator or catalyst is usually heated to initiate polymerization. The resulting polymer can be formed into microspheres. Drug loading can be done during the polymerization process. Polymerization suspension is also referred to as bead or pearl polymerization. Here it is done by heating a monomer or a mixture of monomers as dispersion of droplets in a continuous phase of water. Drops can contain initiators and other adjuvants. Emulsion polymerization differs from polymerization suspension due to its presence initiator in the aqueous phase, which later extends to the surface of the micelles. Bulk polymerization is an advantage of the formation of pure polymers.

II. **Interfacial polymerization:**
   It involves the reaction of various monomers into a visible link between two layers of invisible liquid to form a polymer film that protects the dispersed phase.

F. **Spray Drying Congealing Method:**
These methods depend on the drying of the polymer mist and drugs in the air. Depending on the solvent solution or cooling solution, both processes are called spray drying and cold spraying respectively. The polymer begins to dissolve in the appropriate organic solution such as dichloromethane, acetone, etc. The drug is in a solid state and then disperses in a polymer solution under high homogenization. This spreads and then becomes an atom in the hot air stream. Atomization leads to the formation of small droplets or fine mist in which the solvent evaporates rapidly leading to the formation of microspheres at a distance of size 1-100 µm. Microparticles are separated from hot air by a cyclone separator while solvent particles are removed by a mechanical suspension. One of the great benefits of the process is likely to work under aseptic conditions. The spray drying process is used to wrap various penicillins. Thiamine mononitrate and sulphadiazole are included in the mono- and diglycerides of stearic acid and palmitic acid using spray congealing. The solvent evaporates very quickly but leads to the formation of solid microparticles. The spray drying congealing method schematically represented in Fig 6.
3. **EVALUATION OF MICROBALOONS:**

Empty microspheres are highly processed by solvent evaporation as well emulsion solvent diffusion method to make a circle as an inner hole. These vain microspheres include many examinations.

**FLOATING SYSTEMS:**

a) **FLOATING TIME:**

This can be improved from the buoyancy test introduced from the simulation from the gastrointestinal tract and intestines from stored at 37˚C. The time limit for testing the United States pharmacopeia device from a storage of 900 ml of 0.1N HCL3.

b) **Specific gravity:**

Specific graviscertains gravitational forces include mainly gravity for floating systems can be attested from a disintegration medium that uses benzene as a means of displacing medium.

c) **Resultant weight:**

The weight resulting from the ascent to the bottom, the lower than volume in particular, and the length of time to be cut from the main source to determine the adequacy of the dosage forming drugs.

**SWELLING SYSTEMS:**

a) **Weight gain and water uptake:**

The swelling systems mainly include a performance of dosage forms that can be checked from the water uptake. The dimensional change can be well determined from the measurement in terms of increase in the tablet diameter and measure the thickness of the water and time.

\[ WU = \frac{(WT - WO) \times 100}{WO} \]

Where wt and wo are the weights of their dosage forms at time t and initially and wu indicates water uptake.

**Dissolution tests:**

Dissolution tests mainly done to estimate the drug release from the microballoons. The USP type I dissolution rate testing apparatus is widely used to perform the studies. They can be accomplished in the case of floating hollow by attaching a small, loose piece of non-reacting materials done. However, in the case of swelling systems and drug-released systems relying on long-term reliance on their full exposure, uncontrolled swelling and solubility of drug delivery in water.

**Percentage yield:**

The percentage yield of drug can be determined by using following equation.
Yield= M x 100/Mo  
Where, M = weight of beads Mo = total expected weight of drug and polymer.

**Micromeritic Properties:**
Microballoons were generally evaluated for particle size, shape, bulk density, tapped density, true density, porosity, compressibility index, hausner ration, and angle of repose.

**In vitro buoyancy:**
The required amount of the hollow/empty microsphere is incorporated into 900 mL of 0.1N HCl and shaken for 100 rpm for about 10 hours using dissolution apparatus. Following this process, the layers of buoyant microspheres are pipetted out and separated by filtration. Buoyant microspheres and settled microspheres were dried on the desiccator until a constant weight is obtained. The fraction of the hollow/empty microsphere is weighed, and in vitro buoyancy is determined by the weight of the floating microspheres to the total of floating and sinking microspheres.

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

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

**Applications:**
- Empty microspheres can enhance gastric pharmacotherapy by releasing the drug from the area leading to high concentration of the drug in the gastric mucosa. This process leads to the removal of helicobacter pylori from the tissues of the stomach and helps in the treatment of stomach and intestinal ulcers, gastritis, and stomach.
- They allow for drug withdrawal and release the drug for longer. They are designed as a floating drug delivery system.
- Hollow microspheres of NSAIDs are successful for controlled release and also reduce the side effects of gastric irritation.
- They can be used to deliver drugs through absorption windows such as antivirals, antifungals, and antibiotic agents.
- They provide delivery of drugs directly to the site that are absorbed in the stomach or upper part of the small intestine.
- Floating microspheres can be used as carriers for window-absorbing drugs, these substances, for example antivirals, antifungals and antibiotic agents (sulphonamides, quinolones, penicillin’s, cephalosporins, aminoglycosides and tetracyclines) are taken only in certain areas of the GI mucosa.
- Empty microspheres of non-steroidal anti-inflammatory drugs are very effective in controlled excretion and reduce the overall effect of intestinal irritation. For example, floating microspheres of indomethacin are very useful in rheumatic patients.
- Floating microspheres are particularly effective in the delivery of soluble and insoluble drugs. It is known that as drug dissolution decreases, the current duration of drug dissolution becomes short enough, and then transferred time becomes an important factor affecting drug absorption. With weak drugs that do not dissolve well in alkaline pH, empty microspheres can avoid the risk of melting to be a step that reduces the rate of release, by to prevent those drugs in the stomach. Suspended release is helpful for drugs that are properly packaged with stomach, such as verapamil hydrochloride. The gastroretentive floating microspheres will beneficially alter the absorption profile of the active agent, thus enhancing its bioavailability.
- Empty microspheres can greatly enhance gastric pharmacotherapy with the release of local drugs, which has led to high concentration of the drug in the gastric mucosa, thereby eliminating Helicobacter pylori in the mucosal subcutaneous tissue stomach and enable it to treat stomach and stomach ulcers, gastritis and oesophagitis.

**4. Conclusion:**
The process of absorbing drugs through the intestines varies greatly. Among the drugs currently used in clinics there are small window sores for absorption. Drugs with a small suction window in the upper parts of the gastrointestinal tract with the appropriate candidates for the delivery of anti-retroviral drugs such as enhancing abortion the dosage form extends the duration of drug absorption Without extensive research done to improve control or continuous delivery systems, very few programs are performed, which are kept in the stomach for a long time. A variety of active forms of different therapeutic activities such as anti-inflammatory, antibiotics, anti-ulcer, antidiabetic, is designed for microspheres with promising in vitro and in vivo effects. Empty microspheres is expected to provide a cost-effective, safe and non-invasive structure for the effective management of various diseases.

It is expected that the expansion of strategic thinking strategies and newly developed approaches could reveal much deeper
understanding the mechanisms of abdominal delay. This will ensure a successful development in the abdominal area
the treatment of sustainable microspheres to increase the delivery of molecules in an efficient manner. Moreover, the latter
innovations in drug research will certainly provide real hope for the development of a novel and effective
means the development of this promising drug delivery system.

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