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An incredulous gastro retentive drug delivery system: Review on floating micro-balloons

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Abstract
Floating micro-balloons are a novel drug delivery system designed to protect sensitive drugs from gastric acids and enzymes, releasing them in the gastrointestinal tract. Micro-balloons are gastro-retentive drug delivery system based on non-effervescent approach. Micro-balloons (hollow microspheres) are empty spherical particles without a core having a size less than 200 µm. Thus solubility of the drug is increased, which improves bioavailability and decreases drug waste. This system makes better approach for gastric retention, which would decreases variations in plasma drug concentrations. Multiparticulate system of low density particles can efficiently prolong the gastric retention time of drugs. This review provides an overview of micro-balloons, their formulation methods, characterization, marketed formulations and their applications in controlled drug delivery. We discuss the benefits and limitations of micro-balloons and future directions for research and development.

Keywords: Micro-balloons, gastro retentive drug delivery system, hollow microspheres, floating drug delivery system, non-effervescent

Introduction
A drug substance can be administered in a variety of dosage forms to provide convenient and effective therapy. To maximize therapeutic response, dosage forms can be developed to be administered by alternative delivery routes. Oral dosage forms are typically intended for systemic effects caused by drug absorption through the different epithelia and mucosa of the gastrointestinal tract. Oral route is the most widely using route of administration.

- The oral approach is the most convenient and simplest.
- More Safe and ease of administration.
- Better patient compliance.
- Reduced cost.

Disadvantages include a sluggish onset of action, the possibility of uneven absorption, and medication degradation by gastrointestinal enzymes and secretions. The most common oral dosage forms are tablets, capsules, suspensions, liquids, and emulsions [1].
New drugs can be formulated and developed as oral solid dosage forms such as tablets and capsules as the most effective route of administration. Most of the drugs are administered via oral route to achieve systemic effects [2].

Gastroretentive drug delivery systems (GRDDS): Gastroretentive drug delivery systems (GRDDS) are dosage forms that can remain in the stomach for an extended period of time. GRDDS are suited and advantageous for such medications by boosting absolute bioavailability, therapeutic efficiency, increasing gastric residence time (GRT), probable dose reduction, reducing drug waste, and improving solubility of drugs that less soluble in high pH [3].

Floating drug delivery system: Davis described the floating drug delivery approach in 1968 [3]. These have a lower bulk density than gastric fluids, allowing them to remain buoyant

in the stomach for an extended period of time without influencing gastric emptying rate. While the system floats on gastric contents, the drug is released slowly and at the desired rate. Following drug release, the stomach's residual system is emptied [4]. This results in enhanced GRT, less drug variability, and hence improved bioavailability. Many floating systems have been developed using granules, powders, capsules, tablets, laminated films, beads, and hollow microspheres [5]. The classification of floating drug delivery system (Fig. 1).

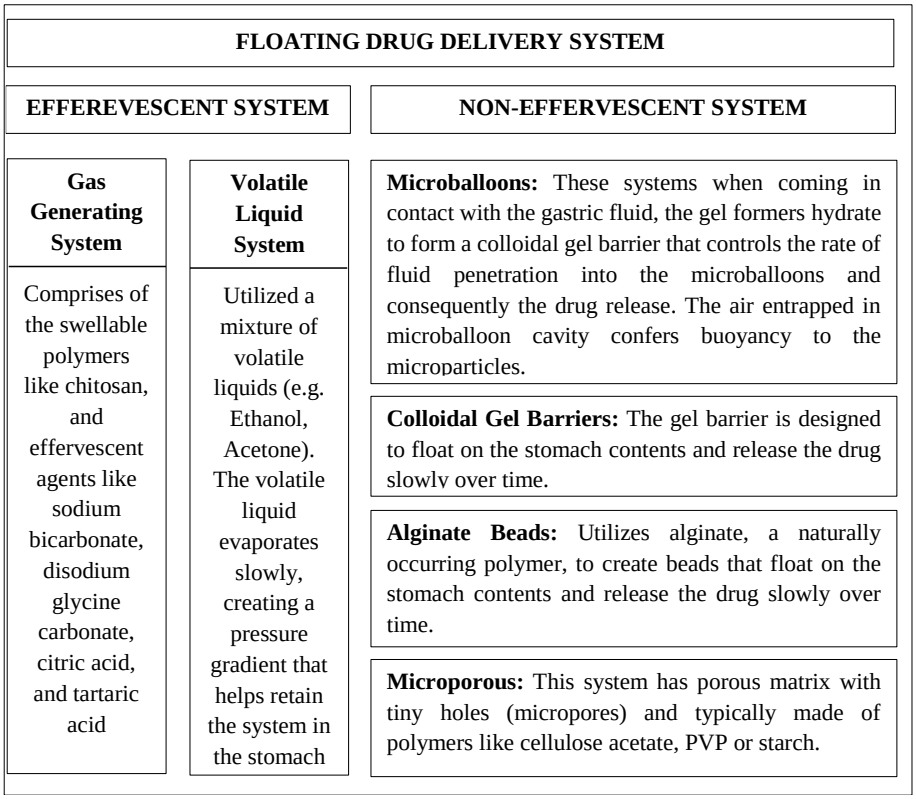

Fig 1: Classification of floating drug delivery system [6, 7]

Micro-balloons

Micro-balloons are gastro-retentive drug delivery system based upon non-effervescent approach. Microballoons (hollow microspheres) are empty spherical particles without a core. These microspheres are free-flowing powders made of proteins or synthetic polymers, with a size of lesser than 200 µm [8].

Microballoons are seen as the favorable buoyant systems, with the distinct advantages that include multiple unit systems and improved floating properties due to the core hollow space within the microsphere [9].

They are prepared using novel techniques such as simple solvent evaporation, emulsion-solvent diffusion, and single and double emulsion, phase separation coacervation, polymerization, spray drying and spray congealing, and hot melt encapsulation [10]. The gradual release of drugs at the optimum rate and improved floating qualities. The type of polymer, plasticizer, and solvents used in the preparation determine the delayed release of the drug at the desired rate as well as the floating properties [11].

Advantages of microballoons

- Improves patient compliance by reducing dose frequency.
- Hollow microspheres reduce material density and improve gastric retention through buoyancy.
- Improved absorption of drugs that dissolve exclusively in the stomach.
- The release drug is controlled over an extended period of time.
- Drug delivery can be targeted to the stomach.
- Microspheres are superior to single unit floating dosage forms because they distribute the drug uniformly and prevent dose dumping [12].
- Avoids gastric irritation by continuous release.
- Short half-life drugs can provide better therapeutic results [13].

Limitations of microballoons

- The controlled release dosage form's release rate can vary depending on circumstances such as diet and gut transit time.
- Different release rates between doses.
- Controlled release formulations have a larger drug load, therefore any compromise of release integrity might cause toxicity.

Mechanisms of micro-balloons

Microballoons are low-density systems with needed buoyancy to float above stomach fluid and remain in the stomach for long period of time. As the dosage form floats over gastric fluid, the drug is released at the optimal rate, resulting in increased gastric retention and less variations in plasma drug concentration. When microballoons come into touch with gastric fluid, the gel develops and polymers hydrate, forming a colloidal gel barrier that regulates the amount of fluid penetration into the dosage form and thus drug release [14]. As the dosage form's outer surface dissolves, the hydrocolloid layer gets hydrated which keeps the gel layer intact. The air entrapped by the swollen

polymer lowers the density than the gastric juice, conferring buoyancy to the microballoons However, a minimum gastric content is required to achieve optimal buoyancy [15]. Materials for preparation of microballoons (Table 1).

Suitable drug candidates for micro-balloons

- Primarily absorbed from upper part of GI and stomach, e.g., calcium supplement, cinnarizine.
- Some nutrients, such as riboflavin and levodopa, have a narrow absorption window in the gastrointestinaltract.
- Drugs which degrade in the colon, such as ranitidine HCl and metronidazole.
- Drugs that disrupt typical colonic bacteria, such as amoxicillin trihydrate.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- Drugs have low solubility at high pH values, e.g., verapamil [13].

Table 1: Materials for preparation of Microballoons [16-18]

Material	Use	Example
Drug	Active Pharmaceutical Ingredient	Metformin, Nizatidine, Pantoprazole, Terbutaline Sulphate, Famotidine
Polymer	Confers buoyancy and controls release	Cellulose acetate, Chitosan, Eudragit, Polyvinyl Acetate, Carbopol
Solvents	Forms hallow microspheres due to their volatility	Ethanol, Dichloromethane (DCM), Acetonitrile, Acetone,
Surfactants	Stabilizers or Emulsifiers	Tween 80, Span 80, SLS
Processing Medium	Used to harden the drug and polymer emulsified droplets.	Liquid paraffin, Polyvinyl alcohol
Hardening agent	Helps to harden the microspheres	N-hexane, Petroleum ether
Crosslinking Agent	Crosslinking of microspheres	Formaldehyde, Glutaraldehyde

Methods of preparation of microballoons

a) Emulsion solvent evaporation method.
b) Emulsion solvent diffusion method.
c) Solvent diffusion-evaporation technique.
d) Spray drying.
e) Multiple emulsion method.
f) Ionotrophic gelation method.

a) Emulsion Solvent Evaporation Method

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 homogeneous polymer solution. The prepared solution is added into 100 ml of liquid paraffin while stirring at 1500 rpm. The so formed emulsion is heated at 35°C for 3hrs. After the formation of emulsion, the acetone or dichloromethane is completely evaporated and formed microspheres are filtered using whatman filter paper. These hollow microspheres possess floating and sustained release properties [19] (Fig. 2).

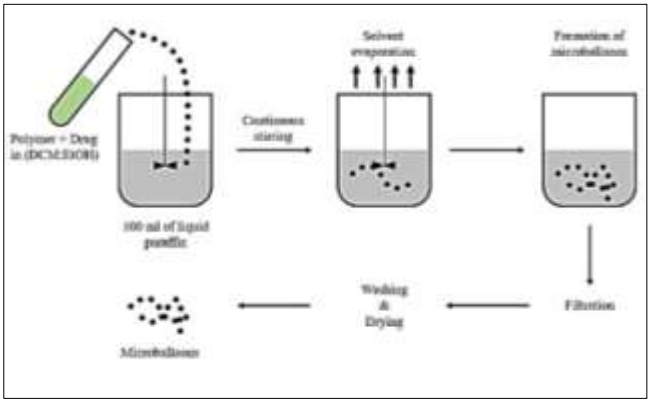

Fig 2: Schematic representation of emulsion solvent evaporation method

b) Emulsion Solvent Diffusion Method

The drug polymer mixture is dissolved in the solution of ethanol: dichloromethane and this mixture is added drop wise to PVA solution. This solution is stirred at 1500 rpm for 1 hour and at various temperatures. In this method, the drug and organic solvent have a stronger affinity than the organic solvent and aqueous solvent. Despite the fact that the organic solvent is miscible, the drug is dissolved in it and then organic solvent is dispersed in the aqueous solvent, resulting in emulsion droplets. The organic solvent diffuses gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse into the droplets by which drug crystallizes [20] (Fig. 3).

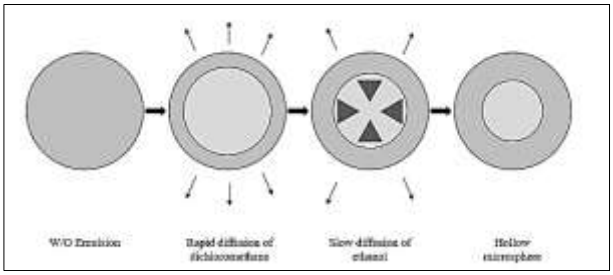

Fig 3: Schematic representation of emulsion solvent diffusion method

c) 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 stirred using propeller agitator for 1 hour for evaporation of organic solution and then filtered it [21] (Fig. 4).

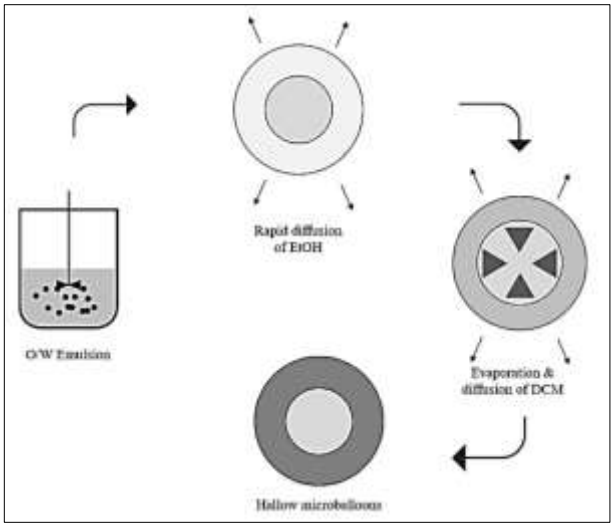

Fig 4: Schematic representation of solvent evaporation diffusion method

d) Spray Drying

Spray drying is the often used process for particle formation and drying. It is an ideal procedure for obtaining the appropriate particle size distribution, bulk density, and particle shape all in one step. First, the polymer is dissolved in a suitably volatile organic solvent, such as dichloromethane or acetone, to generate a slurry. The slurry is then poured into the dry chamber, and a difference in concentration of the solute forms inside the small droplet, with the maximum concentration occurring at the droplet surface. This is due to the fact that the period of solute diffusion is longer than the time it takes for the solvent to evaporate from the droplets during the drying process. A solid shell then forms, resulting in the production of microballoons. Separating the solid products Solid products are typically separated from gases using a cyclone separator, while solvent residues are eliminated through vacuum drying and the products are preserved for later use [22] (Fig. 5).

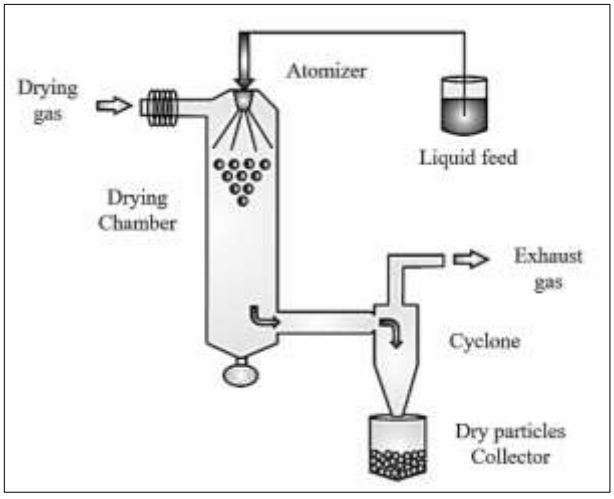

Fig 5: Schematic representation of spray drying method

e) Multiple Emulsion Method

Multiple emulsion method of microspheres preparation involves the preparation of the multiple emulsion or w/o/w type emulsion and it is be suited to water soluble drugs, peptides, proteins and vaccines. The aqueous protein solution is dispersed in a lipophilic organic continuous phase; active constituents is present in this phase. The continuous phase is generally made up of the polymer solution, which contains the protein in the dispersed aqueous phase. The primary emulsion is subjected then to the homogenization before addition to the aqueous solution of the PVA, results in double emulsion. This emulsion is then subjected to solvent removal either by solvent evaporation or solvent extraction [23] (Fig. 6).

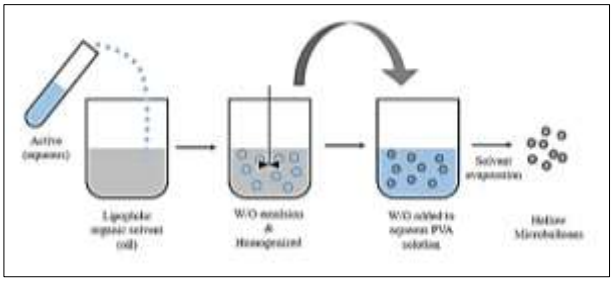

Fig 6: Schematic representation of multiple emulsion method

f) Ionotropic Gelation Method

This method is used to encapsulating of large number of drugs. Sodium alginate a polyelectrolyte which contains anions in the chemical structure is coated on the drug core and also retards drug release rate. This anions forms meshwork structure by combining with polyvalent cations and induce gelation. This approach, an aqueous dispersion of negatively charged polymer together with a gas generating agent (CaCO3 or NaHCO3) was added drop wise into the acidic gelation medium consisting of divalent cations such as Ca^{2+}. As the droplet dips into the acidic gelation medium, gas generating agent effervesces, releasing carbondioxide which then is entrapped in the gel matrix making it lighter then stomach fluids and simultaneously Ca^{2+} present in gelation medium interacts with anionic groups on polymer molecule causing immediate formation of strong aggregation of pairs of helices, leading to strong bead gel structure [23] (Fig. 7).

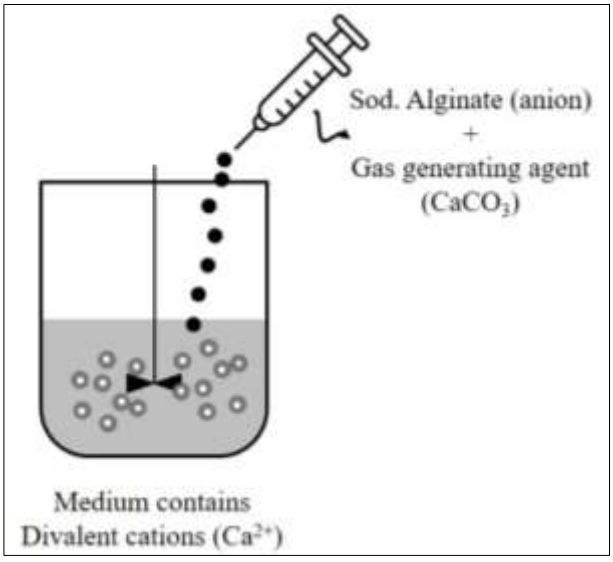

Fig 7: Schematic representation of inotropic gelation method

Evaluation

Particle size analysis

The particle sizes of the microballoons are evaluated using an optical microscope fitted with a calibrated eyepiece

micrometre. It randomly measures the particle diameters of about 300 microballoons and the average particle size was determined using the Edmondson's equation

$d_{mean} = \Sigma nd / \Sigma n$

Where "n" stands for the number of counted microballoons, "d" for the mean size range.

Surface morphology analysis

Scanning electron microscopy (SEM) is used to study the shape and surface morphology of the microballoons [24].

Percentage yield

The percentage yield is found out for all the formulations based on the dry weight of the drug and the polymers taken [25]. The percentage yield can be calculated using the following equation:

$$\text{Percentage yield} = \frac{\text{Total weight of floating microballoons}}{\text{Total weight of drug and polymers taken}} \text{ x } 100$$

Percentage drug entrapment efficiency

Hundred milligrams of microballoons are dissolved in 10 ml ethanol. The samples are then assayed using UV spectrophotometer at λ_{max} after suitable dilution using 0.1N HCl for drug content [26]. Percentage drug entrapment efficiency is calculated using the below equation:

$$\text{Percentage drug entrapment efficiency} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \text{ x } 100$$

***In vitro* buoyancy**

Floating behaviour of microballoons is studied using an USP dissolution test apparatus II. The microballoons (100 mg) is spread on 900 ml of 0.l N HCl (containing 0.02% Tween 80). The medium is agitated at 100 rpm with a paddle, and the temperature is maintained at 37°C. After 12 h, microballoons are collected separately. Then the microballoons are dried and weighed [27].The percentage of microballoons is estimated using below equation:

$$\text{Percentage buoyancy} = \frac{\text{Weight of Microballoons}}{\text{Initial weight of Microballoons}} \text{ x } 100$$

***In vitro* drug release study**

Floating microballoons are evaluated for the *in vitro* drug release studies in simulated gastric fluid. USP dissolution test apparatus II (Paddle type) is used to find out the drug release rate from microballoons. The dissolution test was performed using 900 ml of 0.1N HCl, at 37±0.5 °C and 100 rpm. Microballoons (eq. to 100 mg drug) were accurately weighed and filled in a hard gelatin Capsule and added to the dissolution medium, aliquots (10 ml) are withdrawn at hourly intervals for 12 h. Perfect sink condition is established during the drug dissolution study period by replacing an equivalent volume of dissolution medium. The samples are filtered, and solutions are analysed at λ_{max} using a UV Spectrophotometer [28].

Fourier Transform Infrared Spectroscopy (FTIR)

Drug-polymer interactions were studied by FTIR spectroscopy. The IR spectrum was analysed for the pure drug and drug-loaded microballoons using FTIR. Samples were prepared using KBr (2 mg sample in 200 mg KBr). The scanning range was 400–4000 cm^{-1} and the resolution was 4 [1/cm].

Differential Scanning Calorimetry

The DSC analyses of the pure drug and drug-loaded microballoons is analysed using the DSC to evaluate any possible drug-polymer interaction. The analysis was performed at a rate 100 °C/min from a 200 to 300 °C temperature range under nitrogen flow of 25 ml/min.

Applications of microballoons

- Hollow microspheres can gently boost stomach pharmacotherapy through local drug release, resulting in high drug concentration at the gastric mucosa, eradicating helicobacter pylori from the stomach's submucosal tissue and allowing for the treatment of stomach and duodenal ulcers, gastritis, and esophagitis [29].
- Transilast hollow microspheres are used to create a floating managed drug delivery device [30].
- Hollow microsphere of non-steroidal anti-inflammatory drugs are very effective for controlled release as well if reduces the major side effect of gastric- irritation; for example, floating microballoons of Indomethacin are quite beneficial for rheumatic patients.
- Floating microspheres can greatly enhance the absorption of those drugs which have poor bioavailability and thus it improves absolute bioavailability [31].
- It is recently described that drugs is to be entrapped in hollow microspheres and reduces the fluctuations include Prednisolone, Piroxicam, Lansoprazole, Theophylline, Diltiazem hydrochloride, Celecoxib, Verapamil hydrochloride and Riboflavin [32].
- Microballoons is used to transport the drugs with low absorption windows, for example, antiviral, and antifungal agents (Penicillins, Amino glycosides and Tetracyclines) are absorbed from specific sites of the Gastro intestinal mucosa.

Table 2: Marketed micro-balloon formulations [33]

Brand name	Drug	Company
Nizatidine capsule 150 mg	Nizatidine	Mylan
Protonix	Pantoprazole sodium	Pfizer
Pepcid AC	Famotidine	McNeil consumer pharmaceuticals co
Cytotec	Misoprostol	Pfizer
Pro-Banthine	Propantheline	Kyowa Kirin Ltd
Tazac	Nizatidine	Dr. Reddy Laboratories Ltd.
Inderal	Propranolol HCl	Pellets Pharma Ltd.
Motilium	Domperidone	Nishchem International Pvt. Ltd.
Uniphyl	Theophylline	Kores India Ltd.

Conclusion

According to a recent review, the floating hollow microspheres showed a controlled release delivery system that is retentive, suggesting that this could be a viable method for gastric retention. Microballoons have a low density and enough buoyancy to float over the gastric content and stay there for an extended period.

As the drug floats over the stomach contents, it releases gradually and at the correct rate, which minimizes variations in the plasma drug concentration.

A better way to increase the bioavailability. Optimized microballoons will play a key role in innovative drug delivery, specifically in the areas of diagnostics, gene & genetic materials, safe, targeted, and efficient *in vivo* distribution.

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