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GASTRORETENTIVE MICROBALLOONS: A NOVEL APPROACH FOR DRUG DELIVERY

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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 non-effervescent 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 and marketed products are covered in detail.

INTRODUCTION: Oral administration of drug is most preferred type of route of drug administration [1]. *In-vivo* performance of drug delivery systems can be affected by gastric emptying and frequent dosing of these drugs is required to achieve suitable therapeutic activity [2]. Microballoons are gastro retentive drug-delivery systems with the non-effervescent approach. Microballoons (Hollow microsphere) are in a strict sense, empty particles of spherical shape without a core.

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These microspheres are characteristically free-flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometers [6].

To overcome the impact of gastric emptying a controlled drug delivery system with prolonged residence time in the stomach can be of importance for drugs with an absorption window in the upper small intestine [3]. 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 [4].

TABLE 1: VARIOUS APPROACHES FOR GASTRORETENTIVE DRUG DELIVERY [39, 40, 41, 42]

S. no.	System	Description
1	High density / sinking system	These systems formulated by coating the drug on a heavy core or mixing it with inert materials, density exhibited higher than the density of gastric content. GI transit time of pellets can be enhanced by this method
2	Swelling system	Systems which upon swallowing undergo swelling up to an extent which prevents their exit from the pylorus. Due to this, the formulation can be retained for a prolonged period of time
3	Magnetic system	In this type of dosage form, it comprises a smaller magnetic material and another magnet is applied on the abdomen over the position of the stomach.
4	Bioadhesive / Mucoadhesive system	Gastric retention increased by adhering the bioadhesive system to the gastric mucosal membrane, thus improving the bioavailability
5	Expandable system	A formulation could withstand the gastric emptying when it is larger in size than the pyloric sphincter. For achieving this, three configurations are required: one for oral administration, an expandable gastric form and a part enabling gastric evacuation following complete drug release. Thus, gastro retention can be increased via a combination of substantial dimensions with high rigidity of formulations and mechanical contractions of the stomach
6	Unfoldable system	These systems when swallowed undergo unfolding and enlarge in size, remain lodged at sphincter avoiding its exit from the stomach
7	Low density/ floating system	These systems are formulated with Less density than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate flora prolonged period
a.	Effervescent	Comprises of the swellable polymers like chitosan, and effervescent agents like sodium bicarbonate, disodium glycine carbonate, cytroglycine, citric acid, and tartaric acid
b.	Non-effervescent	Formulated using highly swellable or gel-forming cellulose type hydrocolloids, matrix-forming polymers, and polysaccharides
c.	Microporous	In these formulations Drug reservoir encapsulated within the microporous compartment containing pores. The floating chamber comprising entrapped air provides the delivery system the ability to remain buoyant over the gastric content. The gastric fluid penetrates through the aperture, dissolves the drug and carries the dissolved drug for absorption in the stomach and upper part of the small intestine
d.	Microballoons/hollow Microspheres	These systems when coming in contact with the gastric fluid, the gel formers (polysaccharides/polymers) hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the microballoons and consequently the drug release. The air entrapped in microballoon cavity confers buoyancy to the microparticles. However, minimal gastric content is needed to maintain buoyancy
8	Ion-exchange resin system	In order to achieve gastroprotection, ion-exchange beads are treated with bicarbonate and the negatively charged drug is then bound to the resin. To prevent the loss of carbon dioxide, the beads are entrapped in a semipermeable membrane. On oral administration, the exchange of bicarbonate and chloride occurs in the stomach
9	Raft system	Raft-forming system is one of the most extensively used systems due to the advantage of prolonged and predictable drug delivery provided by this system. This system is effective in releasing the drug in a sustained manner. Raft forming systems are hydrogels at room temperature and undergo gelation on contact with body fluids or with a change in pH. The main objective behind the development of this system is to minimize the dosing frequency and to enhance the efficacy of drug *via* localization at the desired site of action

There are various approaches designed and developed by various researchers like high density (sinking) system or non- floating system, non-effervescent systems, microballoons / hollow microspheres, microporous compartment system, bioadhesive or mucoadhesive drug delivery systems, expandable, unfoldable and swellable systems, super porous hydrogel systems and magnetic systems to achieve gastro retentive drug delivery [4, 5]. Floating or hydrodynamically controlled drug delivery systems are useful and most popular in such applications. Various

gastroretentive dosage forms are available, including tablets, capsules, pills, laminated films, floating microballoons, granules and powders. Floating microballoons have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation. Such systems have more advantages over the single-unit dosage forms.

Microballoons 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 novel techniques involved in their preparation include simple solvent evaporation method, emulsion-solvent diffusion method, single emulsion technique, double emulsion technique, phase separation coacervation technique, polymerization technique, spray drying and spray congealing method and hot melt encapsulation method. The slow release of drugs at the 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 hydroxypropyl methylcellulose, cellulose acetate are used in the formulation of hollow microspheres, and the release of the drug can be modulated by optimizing polymer concentration 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 [7]. Once formulated these microballoons are generally characterized for its quality and efficacy by using different methods including, percentage yield, compatibility studies, micromeritic properties, *in-vitro* buoyancy, scanning electron microscopy, *in-vitro* drug release studies, data analysis of release studies, swelling studies, *in-vivo* studies and entrapment efficiency *etc*.

Mechanism of Drug Release: Microballoon comes 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/ microballoon.

TABLE 2: EXAMPLE OF VARIOUS AGENTS USED FOR FORMULATION OF MICROBALLOON

Drugs as Microballoon formulation	Polymers	Solvents	Processing Medium	Surfactant	Cross linking agents
Nizatidine [8] Metformin [9, 10] Itopride [11] Famotidine [12] Rabeprazole and Amoxicillin [13] Glipizide [14] Pantoprazole [15] Propanolol [16] Cinnarizine [17] Celecoxib [18] Captopril [19] Stavudine [20] Orlistat [21]	Cellulose acetate, Chitosan, eudragit, Acrycoat, methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, polyethylene oxide, Polycarbonates, Acrylic resins, Polyethylene [22]	Ethanol, Dichloromethane (DCM), Acetonitrile, Acetone, Isopropyl Alcohol (IPA), Dimethyl formamide (DMF)[23]	Paraffin, Polyvinyl alcohol, Water	Tween 80, Span 80, SLS	Formaldehyde, Glutaraldehyde

However, minimal gastric content needed to allow proper achievement of buoyancy. Micro-balloon of acrylic resins, eudragit, polyethylene oxide and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.

Methods of Preparation of Microballoons:

A. 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 K_4M 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 [24].

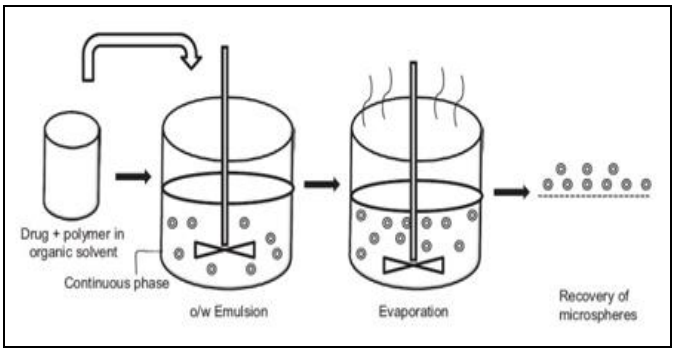

FIG. 1: SOLVENT EVAPORATION METHOD

B. 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 [25].

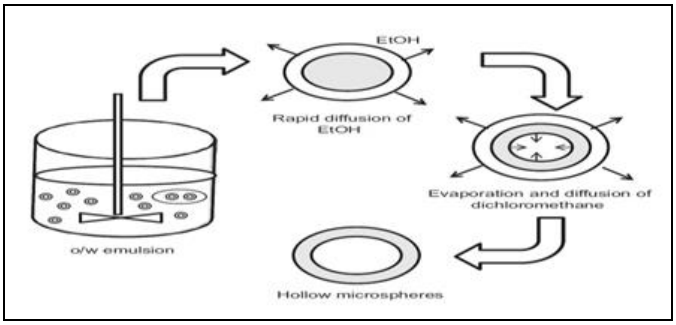

FIG. 2: SOLVENT DIFFUSION METHOD

C. 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 [26].

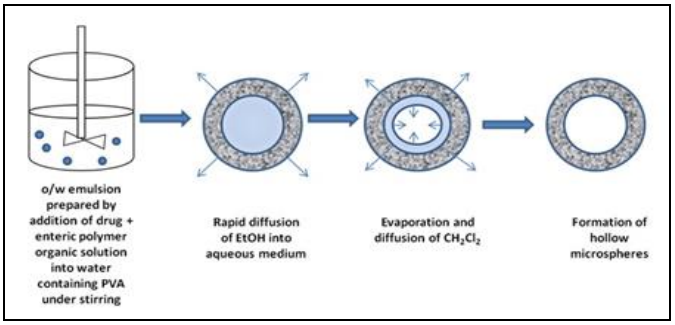

FIG. 3: SOLVENT DIFFUSION-EVAPORATION METHOD

D. 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 [27].

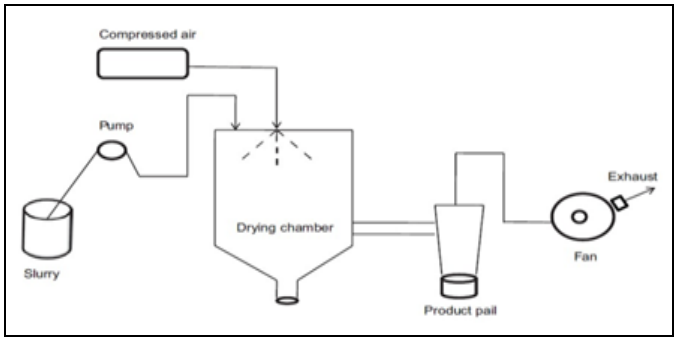

FIG. 4: SPRAY DRYING METHOD

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.

$$\text{Yield} = M/M_o \times 100$$

Where M = weight of beads
M_o = total expected weight of drug and polymer.

2. Micromeritic Properties: [10] 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.

TABLE 3: DETAILS OF MICROMETRICS PROPERTIES

S. no.	Name of Property	Descriptions
1	Bulk density	It is defined as the mass of particles of the material divided by the total volume they occupy. It is calculated by using the formula, Bulk Density = Mass / Volume
2	Tapped density	The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped, and volume or mass readings are taken until little further volume or mass change is observed. Tapped Density = Mass / Change in Volume after tapping
3	Hausner's ratio	The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner (1900–1995) The Hausner's ratio is calculated by the formula, Hausner Ratio (HR) = Tapped Density / Bulk Density
4	Carr's index	The Carr index is an indication of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr. The Carr index is frequently used in pharmaceutics as an indication of the flowability of a powder. In a free-flowing powder, the bulk density and tapped density would be close in value, therefore, the Carr index would be small. It is Calculated using the formula, Carr's Index (CI) = Tapped Density - Bulk Density × 100 / Tapped Density
5	Angle of repose	The angle of repose of a granular material is the steepest angle of descent relative to the horizontal plane to which a material can be piled without slumping. When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area and shapes of the particles, and the coefficient of friction of the material. It is calculated using formula, Angle of repose (θ) = $\tan^{-1}(h/r)$ Where h = Height of Pile and r = radius of Pile

3. Compatibility Studies: Infrared spectrum of the drug, drug-loaded microballoons, blank micro-balloons, physical mixture and empty microballoons are recorded using FTIR [28].

4. *In-vitro* Buoyancy: [29] 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.

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.

$$\text{Buoyancy (\%)} = \{W_f / (W_f + W_s)\} \times 100$$

Where W_f and W_s are the weights of the floating and settled microspheres

5. Scanning Electron Microscopy: [8] 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.

6. *In-vitro* Drug Release Studies: [30] 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.

7. Data Analysis of Release Studies: [31] 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 to find the equation with the best fit using PCP Disso v3 software.

8. Swelling Studies: [32] 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

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.[33]

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

Advantages of Floating Microballoons: [34]

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.
4. Maintenance of a desirable plasma drug concentration by continuous drug release.

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: [34]

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.

Applications of Floating Microballoons: 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 [34]

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 aceto-hydroxamic 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 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.

Recent Advancement: Recently development in hollow microspheres as follow,

1. Yuning Huo *et al*., have developed hollow CdS-TiO_2 microspheres with enhanced visible-light photocatalytic activity [35].

2. Fabrication of hollow carbonate apatite microspheres as bone substitutes have developed by Kazuhiro S *et al*., using calcite microspheres as a precursor [36].

3. Changchun Wang *et al.,* have recently developed in uniform double-shell hollow microspheres from the new polymer backbone transition method as effective acoustic echo imaging contrast agents [37].

4. Kapil Kumar and AK Rai have been opened new doors for the development of hollow microspheres of curcumin as herbal drug delivery systems [38].

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 free-flowing 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.

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CONFLICTS OF INTEREST: Nil

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