MICROBALLOONS: A MODERENSTICS APPROACH FOR GASTRO RETENTIVE DRUG DELIVERY SYSTEM- A REVIEW

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ABSTRACT

The aim of writing this review on microballoons is to assemble the recent literature with special focus on the novel advancements in floating drug delivery system to achieve gastric retention. Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours. The Microballoons delivery systems are useful in such application. Microballoons (Hollow microsphere) promises to be a prospective approach for gastric retention. Microballoons drug delivery systems are based on non-effervescent system. Microballoons are spherical empty particles without core ideally having a size less than 200 micrometer. They are gastroretentive drug delivery systems which provide controlled release properties. The advantages, limitation, applications, list of polymers used in hollow microspheres, characterization of microballons and formulation aspects are covered in detail.

KEYWORDS: Microballoons (Hollow Microspheres), Gastroretentive, Gastric time, Gastric emptying, Buoyancy.

1 INTRODUCTION

Conventional oral dosage forms deliver a specific drug concentration in systemic circulation without offering any control over drug delivery. Controlled release drug delivery system (CRDDS) provide drug release at a predetermined, predictable rate either systematically or locally for a specified period of time and optimizes the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dosing.[1]
The conventional drug delivery system achieves and also maintained the drug concentration in the therapeutically effective range desired for treatment, only when taken numerous times a day. Conventional drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances.\(^\text{[2,3]}\)

1.1 Gastroretentive Drug Delivery Systems (GRDDS)
Dosage forms that can be retained in stomach are called gastro retentive drug delivery systems (GRDDS).

GRDDS are beneficial for such drugs by improving their

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose.
- Reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.
- Apart from these advantages, these systems offer various pharmacokinetic advantages like, maintenance of constant therapeutic levels over a prolonged period.

1.2 Floating Drug Delivery System
Floating systems or Hydrodynamically controlled systems was described by Davis (1968). Floating systems or dynamically controlled systems are low density systems that have sufficiently buoyancy to flow over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This result is an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films, beads and hollow microspheres.\(^\text{[4,5]}\) therapeutic advantages such as.

1. Easily administrations.
2. Low cost of therapy.
3. Patient compliance and flexibility in formulation.
Floating systems can be classified into two systems\[^{[6, 7]}\]

**Effervescent System**
Volatile liquid containing systems
Gas-generating Systems

**Non-Effervescent Systems**
Colloidal gel barrier systems
Micro porous Compartment System
Alginate beads
Hollow microsphere

2. **Microballoons**
Microballoons are gastro retentive drug delivery systems based on non-effervescent approach. Microballoons (Hollow Microsphere) are in spherical empty particles without core. Microballoons is an approach to prolong the gastric retention which have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. These microballoons are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs.\[^{[8]}\]

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 most useful techniques involves 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 are used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer -plasticizer ratio.\[^{[9]}\]
Hollow microspheres are loaded with drug in their outer polymer shell are prepared by a novel solvent evaporation or solvent diffusion/evaporation method to create a hollow inner core. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated solution of Poly Vinyl Alcohol (PVA) that as thermally controlled at 40ºC. After the formation of stable emulsion, the organic solvent is evaporated by increasing the temperature under pressure or by continuous stirring. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The micro balloon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

3 Mechanism of Microballoons
When 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.

4 Materials for Preparation of Microballoons
4.1 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, Ethoxy benzamide, Indomethacin and Riboflavin, Para amino benzoic acid, Furosemide, Calcium supplements, Chlordiazepoxide, Scinnarazine, Riboflavin, Levodopa, Antacids, Ranitidine HCl, Metronidazole and Amoxicillin trihydrate.

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

4.3 Solvents: It should have good volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres. E.g. ethanol, dichloromethane (DCM), acetonitrile, acetone, isopropyl alcohol (IPA), dimethylformamide (DMF).
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 agent.[18]

4.7 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).[19]

5 Method of Preparation

5.1 Solvent Evaporation Method

It is to create the hollow inner core. The 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 studied for the development of such systems include cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinylacetate, carbopol, agar, polyethylene oxide and polycarbonate.

5.2 Emulsion Solvent Diffusion Method

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 in to the droplets by which drug crystallizes.[19,20]
5.3 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.\textsuperscript{[21]}

In this technique polymer is first dissolved in a suitable volatile organic solvent (e.g., dichloromethane, acetone) 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 to the 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{[22]}

6 Factors Affecting Physiochemical Properties of Microballoons

6.1 Stirring Rate

The effects of the stirring rate on microsphere particle size is carried out to observe the effect of agitation speed on the size of the resulting microspheres, formulations are prepared at varying agitation speeds; 300 rpm, 500 rpm, 1000 rpm. The size of the resulting microspheres decreases with increasing agitation, but the increase is not statistically significant. It may be inferred that the agitation speed in the study range is not able to break up the bulk of the polymer into finer droplets.\textsuperscript{[23,24]}

6.2 Temperature of Preparation

The study of optimum preparation temperature with respect to microsphere cavity formation. The solution drug and polymer are poured into an aqueous solution of polyvinyl alcohol at various temperatures, i.e., 20, 30, 40 and 50°C. They conclude that preparation at 20 or 30°C provided porous microspheres having higher porosity with a surface so rough as to crumble upon touching. Although the respective apparent particle densities of the resulting hollow microspheres are low, both buoyancies are low, probably due to easy penetration of the dissolution medium through the porous surface. The roundness of hollow microspheres is prepared at 40°C was close to 1; moreover, surfaces are less rough than those of hollow microspheres prepared at 20 or 30°C. Hollow microspheres is prepared at 50°C exhibited no hollow nature; however, a single large depression occurred on the surface. The hollow
microspheres possesses high apparent particle density and low buoyancy due to the absence of a cavity. Few traces of evaporation are observed on the surface, which is attributable to the rapid evaporation of dichloromethane at temperatures beyond the boiling point (40.2°C). At 40°C, polymers and the drug are co-precipitated, and the shell is formed by the diffusion of ethanol into the aqueous solution and simultaneous evaporation of dichloromethane. In contrast, hollow microspheres is prepared at 50°C demonstrated a single large depression on the surface, which is a consequence of the rapid evaporation of dichloromethane.\(^{25}\)

6.3 Plasticizers
The effect of plasticizer concentration on the surface of microspheres and on the release of the drug. They have found that the addition of plasticizer made the wall of material more elastic and flexible, so that it never get brittle or ruptured under pressure. It is also observed that the release of the drug increased significantly with the increase of plasticizer concentration.\(^{26}\)

6.4 Volume of Aqueous Phase
The effect of various volumes on the formation of hollow microspheres. Volumes of aqueous phase used are 200, 300, 400 and 500 ml they observed that the potential advantage of using large volumes of the external aqueous phase was the reduction of the required stirring times. The solubility of dichloromethane in water is 1% w/v. Using a larger volume (400 to 500 ml), the diffusion of dichloromethane into the aqueous phase, and hence the solidification of particles, occurred faster, when compared to a volume of 200 ml.\(^{27}\)

6.5 Solvent Ratio
The bridging liquid plays a key role in microsphere preparation. When a good solvent diffuses into the poor solvent, which causes the precipitation of the drug and the polymer, a bridge liquid must be present in order to maintain the spherical shape of the microsphere. Too small a volume of the bridging liquid can lead to irregularly shaped microspheres while too large a volume of bridging liquid could prevent the emulsion droplets from solidifying. Therefore, the amount of dichloromethane needs to be carefully controlled.\(^{28}\) The ratio of dichloromethane with ethanol also affects the morphology of the microspheres and the best results with spherical shape are obtained when the ratio of ethanol to dichloromethane is 2:1.\(^{27}\)
6.6 Amount of Polymer and Viscosity
The effect of polymer concentration on in vitro release of aceclofenac from floating microspheres. Increased density of the polymer matrix at higher concentrations results in increased diffusional path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release.\textsuperscript{[29]} The prepared microspheres using a gradually increasing ethyl cellulose concentration in combination with a fixed concentration of hydroxy propyl methyl cellulose (HPMC) to assess the effect of polymer concentration on the size of microspheres. Mean particle size of the microspheres significantly increases with increasing ethyl cellulose. The viscosity of the medium increases at a higher polymer concentration, resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles.\textsuperscript{[24]} When viscosity is increased, the yield of hollow microspheres is decreased, and mean diameter and drug loading amount are increased.\textsuperscript{[30]}

Example- The effect of the drug-to-polymer ratio on the properties of verapamil HCl loaded microspheres. They found that the drug dissolution profile could be slowed down by increasing polymer amount in the formulations, and that particle size, surface characteristics of microspheres, and dissolution rate of verapamil could be modified through the variation of drug-to-polymer ratio.\textsuperscript{[31]}

6.7 Effect of Solvent
The effect of various organic solvents on the formation of microspheres by the solvent evaporation method. Dichloromethane is employed as polar internal organic solvent phase for preparation of microspheres because it is a good solvent for most of polymers and drugs. However, it is observed that the microspheres obtained are not at all spherical in shape. To solve this problem, methanol is used, along with dichloromethane, in the preparation of microspheres. The microspheres so obtained will be spherical, but lack of smooth texture. To avoid this problem, various solvents are critically screened on the basis of the boiling points, such as dichloromethane (39.75ºC), acetone (56.5ºC), methanol (64.7ºC) and ethanol (78.4ºC). It is observed that the boiling point increased from DCM to ethanol and so instead of DCM/methanol, ethanol is tried. Ethanol is a good solvent for most water-soluble drugs and water-insoluble polymers, and it is non-toxic. It remains dispersed as droplets in the oily phase, leading to the formation of a stable emulsion. Ethanol may have worked because it has a high boiling point in relation to other organic solvents (dichloromethane, acetone, methanol.
etc.), which prevents immediate polymer precipitation. The researchers observed that the microspheres so obtained were completely spherical, with a smooth surface.[32]

6.8 Emulsifier Concentration
The effect of emulsifier concentration on particle size is studied by the scientist. They found that the particle size and size distribution were increased when the surfactant concentration was reduced from 1% to 0.25% (w/w). The role of the emulsifier (surfactant) is to decrease the interfacial tension between the dispersed droplets and the continuous phase, as well as to protect the droplets from collision and coalescence. Low emulsifier concentrations may be insufficient to shield the entire droplet surface; droplets are more susceptible to collision and fusion. Also, at higher concentration of emulsifier, lower encapsulation efficiency and larger particle size were obtained, which suggests that the critical micelle concentration had been exceeded, which directly affected emulsion stability. Hence, the optimum concentration of the emulsifier should be identified.[33]

7 Evaluation of Hollow Microspheres
7.1 Percentage Yield
The percentage yield of the hollow microspheres is determined for drug and is calculated using the following equation.[34,35,36]

\[
\text{Yield} = \frac{M}{M_0} \times 100
\]

Where \( M \) = weight of beads
\( M_0 \) = total expected weight of drug and polymer.

7.2 Micromeritic Properties[29]
Hollow microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties.[29] Particle size is measured using an optical microscopy and mean particle size was calculated by measuring 200 to 300 particles with the help of calibrated ocular micrometer. 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 index was calculated using following formula.

\( I = \frac{V_b - V_t}{V_b} \times 100 \)
Where, $V_b$ is the bulk volume and $V_t$ 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.

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

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

### 7.3 *In Vitro* Buoyancy

Fifty milligrams of the hollow microspheres are placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture is stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant microspheres are pipetted and separated by filtration. Particles in the sinking particulate layer are separated by filtration. Particles of both types are dried in a desiccator until constant weight is achieved. Both the fractions of microspheres are weighed and buoyancy is determined by the weight ratio of floating particles to the sum of floating and sinking particles.\[^{37}\]

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

Where, $W_f$ and $W_s$ are the weights of the floating and settled micro particles

### 7.4 Scanning Electron Microscopy

Dry hollow microspheres are placed on an electron microscope brass stub a coated with gold in an ion sputter. Then picture of microsphere are taken by spectro random scanning of the stub. The microspheres are viewed at an accelerating voltage of 20KV.\[^{38}\]

### 7.5 *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 equivalent to required amount of drug is filled into a hard gelatin capsule and place in the basket of dissolution rate apparatus containing dissolution medium. The dissolution fluid is maintained at $37 \pm 1^\circ$C and rotation speed at a specific rpm. Perfect sink conditions prevail during the drug release study. 5 ml samples are withdrawn at each time interval, passes through a 0.25\(\mu\)m membrane filter (Millipore), and analyze using LC/MS/MS method to determine the concentration 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 triplicate."}^{39}

7.6 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 \textit{in vitro} release data to find the equation with the best fit using PCP Disso v3 software."}^{40, 41}

7.7 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) labindia disso 2000) is calculated as per the following formula."}^{42}

\textbf{Swelling ratio} = \frac{\text{Weight of wet formulation}}{\text{Weight of formulations}}

7.8 \textit{In-Vivo} Studies

The \textit{in-vivo} floating behavior can be investigated by X-ray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs. The in-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models (e.g. beagle dogs)."}^{6, 43}

8 Application of Microballoons

8.1 Solid and hollow microspheres 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.

8.2 Hollow microspheres 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.
8.3 These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres are fabricated as a floating controlled drug delivery system.

8.4 The drugs recently reported to be entrapped in hollow microspheres include Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride and Riboflavin, Aspirin, Griseofulvin, Ibuprofen, Terfenadine.

8.5 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 acetohydroxamic acid are formulated for treatment of Helicobacter pylori infection. Hollow microspheres of ranitidine HCL are also developed for the treatment of gastric ulcer.\textsuperscript{[44,45]}

8.6 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 gastroretentive hollow microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.

8.7 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.\textsuperscript{[46]}

8.8 The hollow 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.

8.9 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. [45]

9 Advantages

9.1 Reduces the dosing frequency and thereby improve the patient compliance.

9.2 Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects and despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release. [47]

9.3 Drug releases in controlled manner for prolonged period. [48]

9.4 Site-specific drug delivery to stomach can be achieved. [48]

9.5 Avoidance of gastric irritation, because of sustained release effect. [49]

9.6 Microsphere morphology allows a controllable variability in degradation and drug release. [50]

10 Disadvantages

10.1 The modified release from the formulations.

10.2 Differences in the release rate from one dose to another.

10.3 Dosage forms of this kind should not be crushed or chewed. [50]

11 Future Potential

It is anticipated that various novel products using gastro retentive drug delivery technologies may enhance this possibility. Further investigations may concentrate on the micro balloons concepts.

11.1 Design of an array of gastro retentive drug delivery systems, each having narrow GRT for use according to the clinical need, e.g., dosage and state of disease.

11.2 Determination of minimal cut-off size above that dosage forms retained in the GIT for prolonged period of time.

11.3 Design and development of gastro retentive drug delivery systems as a beneficial strategy for the treatment of gastric, duodenal cancers and treat Parkinson’s disease.

11.4 Development of various anti-reflux formulation utilizing gastro retentive technologies.
11.5 Exploring the eradication of Helicobacter pylori by using various antibiotics.

Table 1: List of Drugs Formulated as Hollow Microballons.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Polymers</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Atenolol</td>
<td>Ethyl cellulose &amp; HPMC</td>
<td>Emulsion solvent evaporation technique</td>
<td>[51]</td>
</tr>
<tr>
<td>2.</td>
<td>Curcumin</td>
<td>Ethyl cellulose, Eudragit S100 &amp; HPMC</td>
<td>Emulsion solvent evaporation technique</td>
<td>[52]</td>
</tr>
<tr>
<td>3.</td>
<td>Tolperisone</td>
<td>Ethyl cellulose (EC), &amp; HPMC 15 cPs</td>
<td>Non-aqueous solvent evaporation technique</td>
<td>[53]</td>
</tr>
<tr>
<td>4.</td>
<td>Famotidine</td>
<td>HPMC and Ethyl cellulose (EC)</td>
<td>Solvent evaporation (Oil-in-water emulsion) technique</td>
<td>[54]</td>
</tr>
<tr>
<td>5.</td>
<td>Captopril</td>
<td>HPMC(K4M) and Ethyl cellulose (EC)</td>
<td>Ionotropic gelation technique</td>
<td>[55]</td>
</tr>
<tr>
<td>6.</td>
<td>Ketoprofen</td>
<td>Eudragit S100 and Eudragit L 100</td>
<td>Emulsion solvent diffusion method</td>
<td>[56]</td>
</tr>
<tr>
<td>7.</td>
<td>Ketorolac trometamol.</td>
<td>Ethyl cellulose, HPMC K4M, Eudragit R100 &amp; Eudragit S100</td>
<td>Emulsion solvent diffusion method</td>
<td>[57]</td>
</tr>
<tr>
<td>8.</td>
<td>Glipizide</td>
<td>Acrycoat S100, Eudragit RS100.</td>
<td>Emulsion solvent diffusion technique</td>
<td>[58]</td>
</tr>
<tr>
<td>9.</td>
<td>Rabeprazole</td>
<td>HPMC K15M and Ethyl cellulose</td>
<td>Emulsion solvent Evaporation</td>
<td>[59]</td>
</tr>
<tr>
<td>10.</td>
<td>Orlistat</td>
<td>Eudragit S</td>
<td>Emulsion solvent Evaporation</td>
<td>[60]</td>
</tr>
<tr>
<td>11.</td>
<td>Esomeprazole</td>
<td>HPMC and Methyl cellulose</td>
<td>Solvent evaporation method</td>
<td>[61]</td>
</tr>
<tr>
<td>12.</td>
<td>Cimetidine</td>
<td>HPMC and Ethyl cellulose</td>
<td>Solvent evaporation method</td>
<td>[62]</td>
</tr>
<tr>
<td>13.</td>
<td>Stavudine</td>
<td>Eudragit RS100</td>
<td>Emulsion solvent diffusion</td>
<td>[63]</td>
</tr>
<tr>
<td>14.</td>
<td>Metformin</td>
<td>Eudragit RS100 and Eudragit RL</td>
<td>Non aqueous solvent evaporation</td>
<td>[64]</td>
</tr>
<tr>
<td>15.</td>
<td>Aceclofenac</td>
<td>Ethyl cellulose</td>
<td>Solvent evaporation</td>
<td>[65]</td>
</tr>
</tbody>
</table>

Table 2: List of Patents for some Hollow Microspheres

<table>
<thead>
<tr>
<th>Patent no.</th>
<th>Year</th>
<th>Patent title</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US0062071971B1</td>
<td>2001</td>
<td>Gastroretentive controlled release microspheres for improved drug delivery</td>
<td>[66]</td>
</tr>
<tr>
<td>US2006/0013876</td>
<td>2006</td>
<td>Novel floating dosage form</td>
<td>[67]</td>
</tr>
<tr>
<td>EP2329810 A1</td>
<td>2011</td>
<td>Gastric retention drug delivery system, preparation method and use thereof</td>
<td>[69]</td>
</tr>
<tr>
<td>US2012/0201892A1</td>
<td>2012</td>
<td>Porous wall hollow glass microspheres as carriers for biomolecules</td>
<td>[70]</td>
</tr>
</tbody>
</table>
7 CONCLUSIONS
In recent review we concluded that the floating hollow microspheres showed gastro retentive controlled release delivery system, promises to be a potential approach for gastric retention. Hollow microspheres are low-density, 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.

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Hollow microsphere promises to be a potential approach for gastric retention.

In future by combining various other strategies, hollow microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

ACKNOWLEDGEMENTS
We would like to express our heartfelt thanks to our beloved parents for their blessings, our teacher's and friends/ classmates for their help and wishes for the successful completion of this review article. The authors have no conflicts of interest that are directly relevant to the content of this review.

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