Microballoons: An Advance Avenue for Gastroretentive Drug Delivery System- A Review

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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.

1 Introduction
Conventional oral dosage forms such as tablets, capsules provide a specific drug concentration in systemic circulation which do not release at the constant rate for prolonged period of time. Controlled release drug delivery system (CRDDS) provides drug release at a precontrolled, predictable rate either systematically or locally for intended duration of time and optimizes the therapeutic effect of a drug by controlling its release into the body with lower and less frequent dosing⁷. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of therapeutic amount of drug concentration in blood with controlled release rate for an extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing the fluctuations of drug concentration and frequency of dosing; it optimized therapy and better patient compliances²³.

1.1 Gastroretentive drug delivery systems (GRDDS)
Dosage forms that can be retained in stomach for longer periods of time are called gastroretentive drug delivery systems (GRDDS).

GRDDS are suitable and beneficial for such drugs by improving their absolute bioavailability, therapeutics efficiency, increase gastric residence time (GRT), possible reduction of the dose, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment¹.
1.2 Floating drug delivery system

Floating drug delivery system was described by Davis (1968).

These are low-density based systems with sufficient buoyancy to float over the gastric contents. While the system is floating on the gastric contents, the drug is released slowly at the constant rate from the system. After release of drug, the residual system is evacuated from the stomach. This result in an increased GRT, reduce fluctuation of drug and thus enhances bioavailability. Many floating systems have been generated based on granules, powders, capsules, tablets, laminated films, beads and hollow microspheres.

It can be classified into two systems.

1.2.1 Effervescent System

Volatile liquid containing systems (Intragastric floating GRDDS)

- Gas-generating Systems (Intra gastric single layer and bilayered floating tablets, Multiple unit type floating pills)

1.2.2 Non-Effervescent Systems

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

2 Microballoons

Microballoons are gastro retentive drug-delivery systems with non-effervescent approach. Microballoons (Hollow microsphere) are in strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometer.

Microballoons are considered as one of the most favourable 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 drug at desired rate and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polyactic acid, Eudragit® S and hydroxy propyl methyl cellulose cellulose acetate are used in the formulation of hollow microspheres, and the release of drug can be modulated by optimizing polymer concentration and the polymer-plasticizer ratio.

Hollow microspheres / microballoons loaded with drug in their outer polymer shell are prepared by a novel methods such as solvent evaporation or solvent diffusion/evaporation to create a hollow inner core. The drug and an enteric acrylic polymer mixture is dissolved in ethanol/dichloromethane solution and it is poured into an agitated solution of Poly Vinyl Alcohol (PVA) that as thermally controlled at 40 ºC. After the formation of stable emulsion, the organic solvent is evaporated from the emulsion by increasing the temperature under pressure or by continuous stirring. The gas phase is generated in the droplet of dispersed polymer by the evaporation of dichloromethane and thus formed the hollow internal cavity in the microsphere of the polymer with drug. The microballoon is continuously float over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

3 Mechanisms of Microballoons

Microballoons are low-density systems that have sufficient buoyancy to float over gastric fluid and remain in stomach for prolonged period of time. As the system floats over gastric fluid, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. When microballoons come in contact with gastric fluid, the gel forms 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 outer 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 makes the density lower than the gastric fluid and confers buoyancy to the microspheres. However, a minimal gastric content needed to allow proper achievement of buoyancy.

Hollow microspheres (Microballoons) of acrylic resins, eudragit, hypromellose, polyethylene oxide, cellulose acetate, polystyrene floatable shells, polycarbonate floating balloons and gelucire floating granules are the recent advancements.

4 Materials for preparation of Microballoons

4.1 Drugs

Drugs with narrow therapeutic window in GI tract, mainly absorbed from stomach and upper part of GIT, locally act in the stomach, degrade in the colon, disturb normal colonic bacteria. E.g. Aspirin, Salicylic acid, Ethoxybenzamide, Indomethacin and Riboflavin, Para amino benzoic acid, Furosemide, Calcium supplements, Chlordiazepoxide, Scinnarazine, Riboflavin, Levodopa, Antacids, Misoprostol, Ranitidine HCI, Metronidazole and Amoxicillin trihydrate.

4.2 Polymers

Cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene.
4.3 Solvents
It should have good volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres eg ethanol, dichloromethane (DCM), 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.

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

5 Method of preparation

5.1 Solvent evaporation method
The polymers for the development of such systems include Eudragit, HPMC KM4 and ethyl cellulose etc. Polymers are mixed with drug and further this mixture is dissolved in the solution of ethanol, acetone or dichloromethane either alone or in combination to get homogenous polymer solution. The resulting solution is poured into 100 mL of liquid paraffin rotating at 1500 rpm. The emulsion is formed and heated at 35°C temperature for 3hr. After the formation of a stable emulsion, the acetone or dichloromethane is completely evaporated and resulting solidified microspheres is filtered using whatman filter paper. This hollow microspheres imparts the floating and sustained properties (Fig 1).

5.2 Emulsion solvent diffusion method
The mixture of drug polymer is dissolved in the solution of ethanol: dichloromethane and this mixture is adding dropwise to polyvinyl alcohol solution. This solution is stirred at 1500 rpm for 1 hour and at different temperature ranges.

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse into the droplets by which drug crystallizes (Fig 2).

5.3 Solvent diffusion-evaporation technique
This technique is with slight modification of both emulsion solvent evaporation method and emulsion solvent diffusion method. Drug, polymers and 0.1% of surfactant such as PEG are mixed in the solution of ethanol: dichloromethane (1:1) at room temperature. This solution is slowly introduced into 80 ml of 0.46% w/v of polyvinyl alcohol as emulsifier. This is stirred...
using propeller agitator for 1 hour for evaporation of organic solution and then filtered it²².

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

5.4 Spray drying

Spray drying is the most widely employed industrial process for particle formation and drying. It is an ideal process where the required particle size distribution, bulk density and particle shape can be obtained in a single step²³.

First of all, polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. to form a slurry. The slurry is then sprayed into the drying chamber, concentration gradient of the solute forms inside the small droplet with the highest concentration being at the droplet surface. This is because the time of the solute diffusion is longer than that of the solvent in the droplets evaporating during the drying process. Subsequently, a solid shell appears leading toward formation of microspheres. Separation of the solid products from the gases is usually accomplished by means of a cyclone separator while the traces of solvent are removed by vacuum drying and the products are saved for later use²⁴ (Fig 3).

6 Factors affecting physiochemical properties of Microballoons

6.1 Stirring rate

It is obvious that the stirring rate affects size of microsphere. 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 over the study range is not able to break up the bulk of the polymer into finer droplets²⁵,²⁶.

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 ºC. They conclude that preparation at 20 or 30 ºC provided porous microspheres.
having higher porosity with a surface so rough as to crumble upon touching. As the preparation temperature increases, particle size decreases. This is because at high temperature, emulsion is less viscous and it becomes much easier for the emulsion to be broken down into smaller droplets at the same power of mixing input. Microballoons prepared at high temperature are found to be a uniform internal pore distribution. Microspheres formed at higher temperature gives very slow release rates after their initial drug release.

6.3 Plasticizers

Due to the addition of plasticizer, it gives elasticity and flexibility to the wall of material so that it never gets brittle or ruptured under pressure. It is also observed that the release of the drug increased significantly with the increase of plasticizer concentration.

6.4 Volume of aqueous phase (Continuous phase)

The effect of various volumes on the formation of hollow microspheres. When the volume of aqueous phase increases the particle size decreases and thus buoyancy increases. Using of large volumes of the external aqueous phase reduces 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.

6.5 Solvent ratio

The bridging liquid plays a key role in microsphere preparation. Very small volume of the bridging liquid gives irregularly shaped microspheres while very large volume of bridging liquid prevents from solidifying of the emulsion droplets. Therefore, the amount of dichloromethane needs to be carefully controlled. The ratio of dichloromethane with ethanol affects the morphology of the microspheres so optimized the ratio which can give best spherical shape. The ratio of ethanol to dichloromethane is 2:1. This gives the best result with spherical shape.

Faster rate of solvent evaporation gives smooth surface, spherical shape and lower encapsulation.

6.6 Amount of polymer and viscosity

Smaller microballoons are formed at a lower polymer concentration and has a larger surface area exposed to dissolution medium giving faster release of drug.

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 the 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 a 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 (39.75 °C), acetone (56.5 °C), methanol (64.7 °C) and ethanol (78.4 °C). It is observed that the boiling point increased from DCM to ethanol and so instead of DCM/methanol, ethanol is tried. Most of the water-soluble drugs and water-insoluble polymers are dissolved in ethanol and it is non-toxic and considered as good solvent. As ethanol have high boiling point in relation to other organic solvents such as dichloromethane, acetone, methanol etc., which prevents immediate polymer precipitation. The researchers observed that the microspheres so obtained were completely spherical, with a smooth surface.

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 is increased when the surfactant concentration is 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. At lower emulsifier concentrations, droplets are more likely to collide and fused to form larger globules; it is insufficient to shield the entire droplet surface. At higher concentration of emulsifier, it reduces the encapsulation efficiency. Hence, the optimum concentration of the emulsifier should be identified.

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.

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

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

7.2 Micromeritic properties

Microballoons are evaluated by their micromeritic properties such as particle shape and size, bulk density, tapped density, Hausner's ratio and flow properties which is determined by carr's index and angle of repose. Particle size is determined by an optical microscopy, and average diameter of particle is calculated with the help of calibrated ocular micrometer (by measuring 200 to 300 particles). 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

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determined by fixed funnel method. The hollow nature of microspheres is confirmed by scanning electron microscopy.

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

\[ I = \frac{V_b - V_i}{V_b} \times 100 \]

Where, \( V_b \) is the bulk volume and \( V_i \) 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:

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

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

7.3 In vitro buoyancy

Appropriate quantity of hollow/empty microspheres are placed in 900 ml of 0.1N HCl. The mixture is stirred at 100 rpm for 8-10 hours in dissolution apparatus. After 8 to 10 hours, the layers of buoyant microspheres are pipetted and separated by filtration. Particles which lies in the layer of sinking particulate are separated by filtration. Particles of both types (buoyant microspheres and settled microspheres) are dried in a desiccator until constant weight is achieved. Both the fractions of empty/hollow microspheres are weighed, and \( \text{In vitro} \) buoyancy is determined by the weight ratio of floating microspheres to the sum of floating and sinking microspheres.

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

Where, \( W_f \) and \( W_s \) are the weights of the floating and settled microspheres.

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 pictures of microsphere are taken by spectro random scanning of the stub. The microspheres are viewed at an accelerating voltage of 20KV.

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 (filled into a hard gelatin capsule) equivalent to dose of drug and place in the basket of dissolution rate apparatus containing dissolution medium. The dissolution fluid is maintained at 37 ± 1 °C and rotation speed at a specific rpm. Perfect sink conditions carry out during the drug release study. Few ml (5 ml) of samples are withdrawn at each time interval and analyzes using Liquid chromatography / Mass spectroscopy method to determine the concentration of microspheres 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.

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 \text{in vitro} release data to find the equation with the best fit using PCP Disso v3 software.

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 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.

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

7.8 In-vivo studies

The \text{in-vivo} studies are performed on suitable animal models example such as rat, beagle dogs etc. The floating behavior can be investigated by radiographical studies using barium sulphate microballoons.

8 Applications of Microballoons

- Microballoons can ameliorate the pharmacotherapy of the stomach through local drug release and it leads to high drug concentrations in the gastric mucosa, thus eliminating Helicobacter pylori from the sub mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.

- These empty microspheres allow 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.

- It is recently described that drugs is to be entrapped in hollow microspheres and reduces the fluctuations include Prednisolone ,Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride and Riboflavin, Aspirin, Griseofulvin, Ibuprofen, Terfenadine.

- Floating microspheres can greatly enhance the absorption of those drugs which have poor absorption.

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bioavailability and thus it improves absolute bioavailability.\textsuperscript{46,47}

- Floating microspheres are site specific drug delivery especially for those drugs which are specifically absorbed from stomach or the proximal part of small intestine.

- 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 within the stomach for more than 10 hours e.g., Metoclopramide and glipizide loaded chitosan microspheres.\textsuperscript{48}

- Microballoons can be used to transport the 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.

- Empty microspheres of NSAIDS drugs are very successful for controlled release as well as it reduces the side effect of gastric irritation; for example floating microspheres of Indomethacin is quite beneficial for rheumatic patients.\textsuperscript{47}

9 Advantages

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

- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects, and despite the first-pass pass effect because fluctuation in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.\textsuperscript{49}

- Hollow microspheres are used to decrease material density and Gastric retention time is increased because of buoyancy.

- Enhanced absorption of drugs which solubilize only in stomach.

- Drug releases in controlled manner for prolonged period.\textsuperscript{50}

- Site-specific drug delivery to stomach can be achieved.\textsuperscript{50}

10 Disadvantages

- The modified release from the formulations.

- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.

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

- Controlled-release 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.

- Dosage forms of this kind should not be crushed or chewed.\textsuperscript{52}

11 Future Potential

It is expected that various new products using gastro retentive drug delivery technologies may magnify this possibility. Further investigations may concentrate on the microballoons concepts:

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

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

- 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.

- Development of various anti-reflux formulation utilizing gastro retentive technologies.

- Exploring the eradication of Helicobacter pylori by using various antibiotics.

12 Recent researches on microballoons

(Some of drugs are formulated in Microballoons as shown in table 1.)

12.1 Based on various literature surveyed, it is concluded that microballoons gastro retentive drug delivery system improves the bioavailability of those drugs with poor bioavailability.

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because of site specific absorption from the upper part of GIT. Therefore maximizing the absorption and formulated into microballoons.

12.2 Formulated sustained release microspheres of Acarbose were prepared by solvent evaporation method to achieve high entrapment efficiency. It is concluded from the study that loading of acarbose into microsphere shown the sustained release of drug and it was affected by the pH of the dissolution medium. It improves therapeutic response, patient compliance, minimizes side effects by reducing dose frequency. Thus increases patient compliance.

Table 1: List of drugs formulated as microballoons

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Polymers</th>
<th>Method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Atenolol</td>
<td>Ethyl cellulose &amp; HPMC</td>
<td>Emulsion solvent evaporation</td>
<td>56</td>
</tr>
<tr>
<td>2.</td>
<td>Curcumin</td>
<td>Ethyl cellulose, Eudragit S100 &amp; HPMC</td>
<td>Emulsion solvent evaporation</td>
<td>57</td>
</tr>
<tr>
<td>3.</td>
<td>Tolperisone</td>
<td>Ethyl cellulose (EC), &amp; HPMC 15 cPs</td>
<td>Non-aqueous solvent evaporation</td>
<td>58</td>
</tr>
<tr>
<td>4.</td>
<td>Famotidine</td>
<td>HPMC and Ethyl cellulose (EC)</td>
<td>Solvent evaporation technique</td>
<td>59</td>
</tr>
<tr>
<td>5.</td>
<td>Captopril</td>
<td>HPMC(K4M) and Ethyl cellulose (EC)</td>
<td>Ionotropic gelation technique</td>
<td>60</td>
</tr>
<tr>
<td>6.</td>
<td>Ketoprofen</td>
<td>Eudragit S100 and Eudragit L 100</td>
<td>Emulsion solvent diffusion method</td>
<td>61</td>
</tr>
<tr>
<td>7.</td>
<td>Ketaolac</td>
<td>Ethyl cellulose, HPMC K4M, Eudragit R100</td>
<td>Emulsion solvent diffusion method</td>
<td>62</td>
</tr>
<tr>
<td>8.</td>
<td>Glipizide</td>
<td>Acrycoat S100, Eudragit RS100.</td>
<td>Emulsion solvent diffusion</td>
<td>63</td>
</tr>
<tr>
<td>9.</td>
<td>Rabeprazole</td>
<td>HPMC K15M and Ethyl cellulose</td>
<td>Emulsion solvent Evaporation</td>
<td>64</td>
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<tr>
<td>10.</td>
<td>Orlistat</td>
<td>Eudragit S</td>
<td>Emulsion solvent Evaporation</td>
<td>65</td>
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<td>11.</td>
<td>Esomeprazole</td>
<td>HPMC and Methyl cellulose</td>
<td>Solvent evaporation</td>
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<tr>
<td>12.</td>
<td>Cimetidine</td>
<td>HPMC and Ethyl cellulose</td>
<td>Solvent evaporation</td>
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<td>13.</td>
<td>Stavudine</td>
<td>Eudragit RS100</td>
<td>Emulsion solvent diffusion</td>
<td>68</td>
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<tr>
<td>14.</td>
<td>Metformi</td>
<td>Eudragit RS100 and Eudragit RL</td>
<td>Non aqueous solvent evaporation</td>
<td>69</td>
</tr>
<tr>
<td>15.</td>
<td>Aceclofenac</td>
<td>Ethyl cellulose</td>
<td>Solvent evaporation</td>
<td>70</td>
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</table>
12.3 Formulated floating microspheres of Eudragit S100 containing Clarithromycin drug. The resulting microsphere shown the prolonged release of drug and more than 80% of the drug was entrapped and released in 12 hours. Different process variable were optimized to provide the best results. The optimized concentration of surfactant, temperature, stirring speed was found to be 0.75%, 37 °C, 400 rpm respectively.

12.4 Developed once daily sustained release floating dosage form of Salbutamol sulfate coated with Eudragit RL100 using solvent evaporation method and it's in vitro characterization. This literature surveyed concluded that entrapment efficiency was increased as the concentration of polymer increased. It remained buoyant in gastric fluid containing surfactant for 8-12 hours in vitro. The average particle size increased and rate release of drug decreased at higher polymer concentration. In vitro drug release studies were carried out in both acidic medium pH 1.2 and pH 6.8 buffers for 12 hours and observed that drug release was faster in pH 6.8 due to polymer solubility in pH 6.

Table 2: List of Patents for some Microballoons (Hollow Microspheres)

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<thead>
<tr>
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<tr>
<td>US0062071971B1</td>
<td>2001</td>
<td>Gastroretentive controlled release microspheres for improved drug delivery</td>
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<tr>
<td>US2006/0013876</td>
<td>2006</td>
<td>Novel floating dosage form</td>
<td>72</td>
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<td>US2010/0015224A1</td>
<td>2010</td>
<td>Programmable buoyant delivery technology</td>
<td>73</td>
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<tr>
<td>EP2329810 A1</td>
<td>2011</td>
<td>Gastric retention drug delivery system, preparation method and use thereof</td>
<td>74</td>
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<tr>
<td>US2012/0201892A1</td>
<td>2012</td>
<td>Porous wall hollow glass microspheres as carriers for biomolecules</td>
<td>75</td>
</tr>
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</table>

13 Patented Microballoons (Hollow Microspheres) (Table 2)

14 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.

Microballoons are low-density, sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate when it floats over gastric contents resulting reduced fluctuations in plasma drug concentration.

It is efficient means of enhancing the bioavailability. Optimized microballoons 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.

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16 Conflict of interests

The authors have no conflicts of financial interest that are directly relevant to the content of this review.

17 Author’s contributions

RK and SK carried out literature review and draft the manuscript. AC, PKG and VKS participated in collection of data and arranged in tabular form. All authors read and approved the final manuscript.

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