HOLLOW MICROSPHERES: AN EMERGING APPROACH IN THE FIELD OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT
The problem of short gastric residence time encountered with an oral CR formulation. One of the technologies to overcome this problem is formation of floating drug delivery systems. Hollow microspheres represent this type of system. Hollow microspheres loaded with drug in their outer polymer shelf. The problem of short gastric residence time with an oral CR formulation can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. Hollow microspheres as gastroretentive dosage forms precisely control the release rate of target drug to a specific site and facilitates an enormous impact on health care. Optimized multi-unit floating microspheres are expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the effective management of diverse diseases. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Gastroretentive drug delivery system offers several advantages besides providing better bioavailability to poorly absorbed drugs and a required release profile thus attracting interest of pharmaceutical formulation scientists. The purpose of this review is to focus on the recent advances in the field of formulation, characterization, evaluation and applications of floating microspheres in the area of gastroretentive dosage forms. This review attempts to bring more insight into recent advances in methods of fabrication techniques and applications of hollow microspheres.
INTRODUCTION:
The goal of any drug delivery system is to provide a therapeutic amount of drug at the proper site in the body and then maintain the desired drug concentration [1]. Conventional drug delivery system maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day [2]. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. Although a lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. [3]. Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption pioneered the idea of development of Gastroretentive drug delivery system (GRDDS) [4]. The ability of gastroretentive systems to remain in the gastric region for a longer period significantly prolong the gastric retention time of drugs. Improved bioavailability, reduction in drug waste and improvement in solubility of drugs that have limited solubility in high pH environment can be achieved by prolonging gastric retention of drugs. [5,6].

It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. [7,8] Gastroretentive delivery systems (GRDS), however, are not suitable for drugs that may cause gastric lesions, e.g., non-steroidal anti-inflammatory agents, Drug substances that are unstable in the strong acidic environment of the stomach are not the suitable candidates to be incorporated in such systems. [9] Floating Drug Delivery Systems (FDDS) first described by Davis (1968), are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastroretention time and reduces fluctuations in plasma drug concentration. Hollow microspheres are gastroretentive drug delivery systems based on non-effervescent approach. They are spherical empty particles without core. They possess the unique advantages of multiple unit systems and their center hollow space imparts good floating properties making them promising buoyant systems. [10]

ADVANTAGES:
Hollow microspheres offer various advantages including:
1. Improved patient compliance and convenience owing to less frequent dosing.
2. Decreased local and systemic side effects by reduction in fluctuation in steady state level.
3. Increased drug utilization by decreased total amount of drug used.
4. Avoid drug accumulation on chronic dosing.
6. Avoidance of gastric irritation due to sustained release effect. [12]

**DISADVANTAGES:**

Although hollow microspheres have a number of potential advantages, their use can be limited due to the following:

1. Risk of dose dumping due to increase quantity of drug release which in turn leads to toxicity.
2. Need for additional patient education and counseling.
3. Stability problems due to complexity.
4. More rapid development of tolerance. [13]
5. Often more expensive than conventional dosage forms because of the use of polymers, biomaterials, and special manufacturing techniques. [14]
6. Reduction in systemic availability.
7. In case of oral sustained release formulation, drug release period influenced by gastrointestinal residence time.
8. Reduced potential for accurate dose adjustment.
9. Retrieval of the drug is difficult in case of toxicity / poisoning / hypersensitive reaction. [15]

**APPROACHES TO GASTRIC RETENTION**

Various approaches have been reported to achieve gastric retention of an oral dosage form. These include.

**Hydrodynamically balanced systems**

In hydrodynamically balanced systems, drug with gel-forming hydrocolloids are meant to remain buoyant over the stomach content. This prolongs gastric retention time and maximizes the amount of drug that reaches its absorption sites. These hydrocolloids on contact with gastric fluid, hydrates and forms a colloid gel barrier around its surface. [16]

**Effervescent systems**

The gas generating agents such as carbonates (e.g., sodium bicarbonate) and other organic acid (e.g., citric acid and tartaric acid) are utilized in the formation effervescent systems. The density of the present system is reduced due to the production of carbon dioxide by the reaction of gas generating agents with gastric acid, thus allowing the system to float on the gastric fluid. [17]

**High density systems**

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI
transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. [18]

**Raft systems**
Raft forming systems incorporate alginate gels. These have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating [19]. These systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of *helicobacter pylori* (*H. Pylori*) infections in the GIT [20, 21].

**Low-density systems**
Floating systems are based on low density approach. Floating drug delivery systems by virtue of their bulk density lower than gastric fluids (<1 g/ml), float over the gastric fluid and release the drug slowly for a longer period of time. They are prepared by incorporating low-density materials, entrapping oil or air. Most are multiple unit systems and are also called “microballoons” because of their low-density core. [22]

**Ion exchange resins:**
Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly. [23]

**Osmotic regulated systems:**
It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment. [24]
FACTORS AFFECTING GASTRIC RETENTION

**Density:** Density of the dosage form should be less than the gastric contents (1.004 gm/ml).

**Size:** Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to with those with a diameter of 9.9 mm.

**Shape:** The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT, 90 to 100% retention at 24 hours compared with other shapes.

**Fed or Unfed State:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

**Single or multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms [25].

**Nature of the meal:** Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.

**Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

**Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

**Gender:** Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down [26].

**Age:** Elderly people, especially those over 70 years have a significantly longer GRT.

**Posture:** GRT can vary between supine and upright ambulatory states of the patients. 1.2.12

**Diseased state of the individual:** biological factors also affect the gastric retention e.g. Crohn’s disease, gastrointestinal diseases and diabetes.

**Concomitant drug administration:** Anti-cholinergics like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

**TECHNIQUES FOR PREPARATION OF HOLLOW MICROSPHERES**

Various methods have been developed for the preparation of hollow microspheres. These include:
Solvent evaporation method
In this method, the drug and polymer are dissolved in an organic phase (usually methylene chloride) and dispersed in an excess amount of aqueous continuous phase, with the aid of an agitator to form an emulsion. Depending upon the hydrophilicity or the hydrophobicity of drugs, different methods are used to prepare microspheres by solvent evaporation technique. [27]

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. [28]
Ionotropic Gelation Method

Ionotropic gelation is based on the ability of poly electrolytes to cross link in the presence of counter ions to form beads. Since, the use of alginates, gellan gum, chitosan and carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose. The natural poly electrolytes in spite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. [29]

Figure 3: Ionotropic Gelation Method

EVALUATION OF MICROSPHERES:
Micromeritic Properties:
The microspheres were characterized for their micromeritic properties, such as particle size, tapped density, bulk density, compressibility index and flow properties. The size was measured using an optical microscope, and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer. The bulk density apparatus was used to determine the tapped density, bulk density and percent compressibility index as follows: [30]

\[
\text{Bulk Density} = \frac{\text{Weight of microspheres}}{\text{Volume of microspheres before tapping}}
\]

\[
\text{Tapped density} = \frac{\text{Weight of microspheres}}{\text{Volume of microspheres before tapping}}
\]

\[
\text{% Compressibility Index} = \frac{\text{Tapped density} - \text{Untapped density}}{\text{Tapped density}} \times 100
\]

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**Percentage yield**
Percentage yield of floating microspheres is calculated by dividing actual weight of product to total amount of all nonvolatile components that are used in the preparation of floating microspheres and is represented by following formula: [31,32]

\[
\text{Percentage yield} = \frac{\text{Actual weight of floating microspheres}}{\text{Total weight of excipients and drug}} \times 100
\]

**Drug entrapment efficiency**
Estimation of drug content in floating microspheres can be carried out by dissolving the weighed amount of crushed microspheres in required quantity of 0.1 N HCl and analysed spectrophotometrically at a particular wavelength using the calibration curve. Each batch should be examined for drug content in a triplicate manner. The entrapment efficiency of floating microspheres is calculated by dividing the actual drug content by the theoretical drug content of microspheres. [33, 34]

**Floating behavior**
Appropriate quantity of the floating microparticulates is placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0), the mixture is stirred with a magnetic stirrer. The layer of buoyant microparticulate is 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. [35]

\[
\text{Buoyancy (%)} = \frac{\text{Wf}}{\text{Wf} + \text{Ws}} \times 100
\]

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

**In-vitro drug release studies**
The release rate of floating microspheres is determined using United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug is filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. 500 ml of the SGF containing 0.02% w/v of Tween 20 is used as the dissolution medium. The dissolution fluid is maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples are withdrawn at each 30 min interval, passed through a 0.25 μm membrane filter (Millipore), and analyzed 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.

**In-vivo studies**
The *in-vivo* floating behavior can be investigated by X-ray photography of hollow microparticulate loaded with barium sulphate in the stomach of beagle dogs. The *in-vitro* drug release studies are
performed in a dissolution test in a dissolution media. The *in-vivo* plasma profile can be obtained by performing the study in suitable animal models. [30, 36, 37].

REFERENCES:


