A Comprehensive Review on Hollow Microspheres Gastroretentive Drug Delivery System

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Abstract: The issue of oral CR formulations having a brief stomach residence period. Development of floating medicine delivery devices is among the techniques being used to solve this issue. This kind of system is represented by hollow microspheres. Hollow microspheres with a polymer shelf and a pharmacological load inside. With these approaches, the issue of a short stomach residence time with an oral CR formulation can be resolved. These systems may floatable on the gastric contents because of their bulk density. Hollow microspheres as gastro-retentive dosage forms enable a significant impact on health care by carefully controlling the target drug's release rate to a specified spot. Improved multi-unit floating microspheres are anticipated to offer clinicians a new option for a cost-effective, secure, and more bioavailable formulation in the efficient management of a variety of disorders. The design of novel controlled and delayed release oral formulations is made possible by these technologies, further pushing the boundaries of pharmaceutical research and development. In addition to improving the bioavailability of medications that are poorly absorbed and requiring a needed release profile, the Gastro-retentive drug delivery system has various other benefits that have pharmaceutical formulation experts interested. The focus of this paper is on current developments in the preparations, characterisation, assessment, and use of floating microspheres as gastro retentive dosage forms. This review aims to shed additional light on recent developments in hollow microsphere production methods and applications.

Index Terms: Floating microspheres, hollow microspheres, gastric retention.

INTRODUCTION

Any drug delivery system's objective is to administer a medicinal dose of the medication to the right location in the body and then to sustain the desired amount of drug [1]. Only when taken multiple times daily does Using a traditional medication delivery technique, the medicine dosage is maintained inside that therapeutically necessary range. [2]. Due to the simplicity of handling and administering oral dosage forms, a high level of patient compliance has been noted. Despite significant improvements in oral controlled drug delivery over the past few decades, these systems have had mixed results when used with medications that have poor GIT absorption windows. One of the key difficulties in creating an oral controlled medication delivery system is modifying the GI transit time. [3] The degree of GIT absorption affects how well an oral medication delivery method works. As a result, the invention of the GRDDS was sparked by the notion of improving medication absorption [4]. The gastric retention duration of medications is greatly extended by gastro-retentive systems' capacity to stay in the stomach area for a longer time. By extending the time that medications are retained in the stomach, it is possible to increase their bioavailability, decrease drug waste, and enhance the solubility of pharmaceuticals whose solubility is limited in high pH environments. [5,6]. It can be used to administer medications locally to the stomach and nearby small intestines. Gastro retention aids in improving the accessibility of novel drugs with fresh therapeutic opportunities and significant patient advantages. [7,8] However, GRDS are not appropriate for medications that might result in stomach lesions, such as NSAIDs, Medication compounds which are unsteady in the stomach's highly acidic environment are not good candidates for inclusion in such systems. [9] The medicine is delivered slowly at the correct pace as the apparatus floats over the contents of the stomach, lengthening gastro-retention duration and minimising changes in plasma drug concentration. Hollow microspheres are non-effervescent drug delivery methods that are gastro-retentive. They are round, empty, and lack a core. They are promising buoyant systems because they have the special benefits of numerous unit systems and their core hollow area, which gives off strong floating capabilities. [10]

Advantages:

1. Better patient comfort and compliance as a result of less frequent dosing.
2. Less variability in the steady state level results in less local and systemic negative effects.
3. A rise in drug usage offset by a fall in overall drug use.

4. Prevent medication build up from long-term dosage.
5. 5. Lowering health care expenditures through more effective therapy and quicker recovery times. [11]
6. The continuous release effect prevents stomach discomfort. [12]

Disadvantages:

1. Risk of dosage dumping due to increased drug toxicity from increased drug release.
2. The demand for more patient counselling and education.
3. Complexity-related issues with stability.
4. Increased tolerance development. [13]
5. Because they employ specialised production processes, biomaterials, and polymers, they are frequently more expensive than traditional dosage forms. [14]
6. A decrease in the availability of systems.
7. The gastrointestinal residence duration affects the medication release period in the case of oral sustained release formulations.
8. Less chance for precise dosage adjustment.
9. Drug retrieval is challenging in cases of toxicity, poisoning, or hypersensitivity response. [15]

Approaches to Gastric Retention:

It has been claimed that many methods can be used to make an oral dose form remain in the stomach. These consist of

Hydrodynamically balanced systems:

Drugs that include gel-forming hydrocolloids are intended to float above the contents of the stomach in hydrodynamically balanced systems. This optimises the quantity of medication that reaches its absorption sites while extending the length of stomach retention. These hydrocolloids hydrate when they come into touch with stomach fluid, creating a colloid gel barrier on their surface. [16]

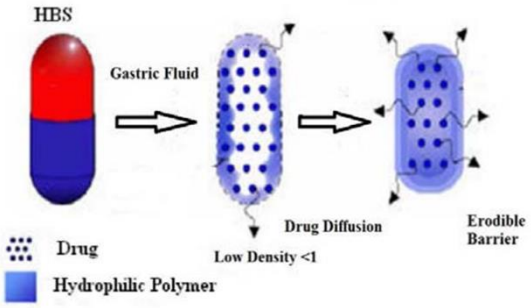

Fig.1: Hydrodynamically balanced system

Effervescent Systems:

The creation of effervescent systems makes use of gas-generating substances such carbonates (for example, NaHCO3) and other organic acids. Due to the reduction in density of the current system caused by the creation of carbon dioxide as a result of gas producing agents reacting with stomach acid. [17]

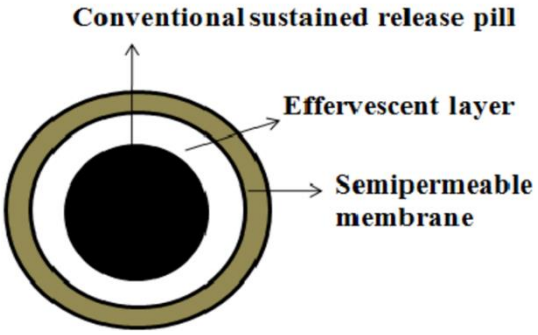

Fig.2: Effervescent System

High Density Systems:

Sedimentation was already employed as a preservation method for pellets tiny enough to be kept in the anteriorly or folding of the stomach body near to the pyloric region—the portion of the organs with the lowest position when the body is upright. Dense pellets that get trapped in rugae and weigh around 3g/cm-3 also tend to be subjected to peristaltic movements of the stomach wall. With pellets, the GI transit time may be extended from an average of 5.8 to 25 hrs, with particles size showing less of an effect than density. [18]

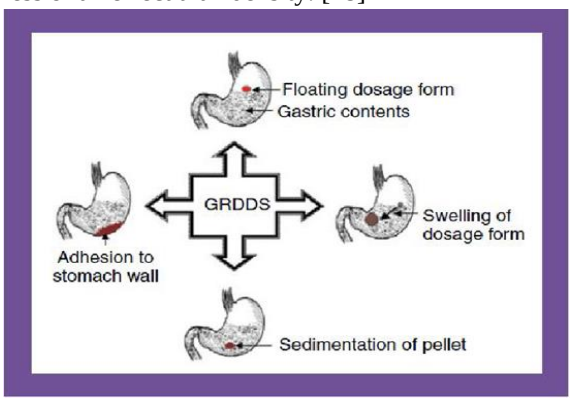

Fig.3: Different types of gastroretentive forms

Raft Systems:

Systems for creating rafts use alginate gels. These include a carbonate component, which, when exposed to stomach acid, causes bubbles to develop in the gel, allowing them to float [19]. Antacid administration and medication delivery for gastrointestinal infections and illnesses have drawn a lot of interest to these systems. The production of a viscous cohesive gel in contact with stomach

fluids, where each section of the liquid expands to create a continuous layer known as a raft, is one of the mechanisms involved in the formation of rafts. [19,20,21]

Low Density Systems:
Low density is the foundation of floating systems. Due to their lower bulk density than gastric fluids (1 g/ml), floating drug delivery devices float above the stomach fluid and release the medication gradually over a longer period of time. They are made by adding low-density materials and enclosing air, oil, or both. The majority have several units and are also referred to as "micro-balloons" owing of its core's lower density. [22]

Ion exchange resin:
Bicarbonate is added to ion exchange resins, and then a negatively charged medication is attached to the resin. To prevent the quick loss of carbon dioxide, the resulting beads are subsequently enclosed in a semi-permeable membrane. Chloride and bicarbonate ions are exchanged once they reach the stomach's acidic environment. This interaction causes carbon dioxide to be released and retained in the membrane, which causes beads to rise to the top of the stomach's contents and form a layer of resin beads that floats in contrast to the uncoated beads, which sink fast. [23]

Osmotic regulated systems:
It consists of a bio-erodible capsules, an inflated floating base, and a medication delivery system regulated by osmotic pressure. The capsule immediately breaks down in the stomach, releasing the osmotically controlled intragastric medication administration device. A fluid that gasifies at body temp inflates a hollow, flexible polymeric bag that is created inside the inflatable support. The osmotically controlled drug delivery system is made up of the medication reservoir partition and the osmotically active compartment. [24]

Gastric retention-related factors include:
Density: The dosing form's thickness must be lower than the stomach contents' (1.004 g/ml) density.

Size: The GRT of tablet formulations components having a diameter of more than 7.5 mm was discovered to be more than that of dosage form units with a diameter of 9.9 mm.

Fed or Unfed State: GI motility during a fast is characterised by bursts of vigorous motor function or migrating myoelectric complexes (MMC), which happen around every 1.5 to 2 hours. However, MMC is sluggish and GRT takes a lot longer in the fed condition.

Caloric Content: With a meal strong in carbohydrates and fats, GRT can be extended by 4 to 10 hours.

Feeding frequency: Because of the low intensity of MMC, the GRT can increase by almost 400 minutes when many meals are given in succession as opposed to a single meal.

Gender: Generally speaking, ladies empty their stomachs more slowly than guys do. Depression reduces stomach emptying rates whereas stress speeds them up [26].

TECHNIQUES FOR PREPARATION OF HOLLOW MICROSPHERES

Solvent evaporation method:
This procedure creates an emulsion by dissolving the medication and polymer in an organic phase (often methylene chloride) and dispersing them in too much aqueous continuous phase. In order to manufacture microspheres using the solvent evaporation process, various techniques are utilised depending on the hydrophilicity or hydrophobicity of the medicines. [27]

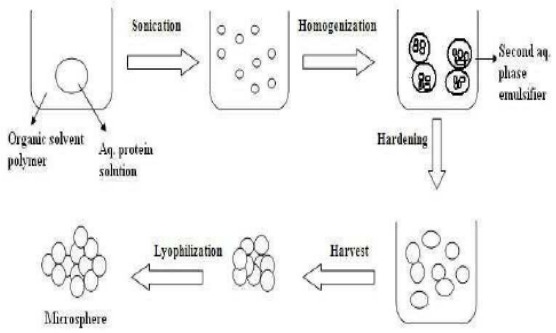

Fig.4: Preparation of Microspheres using solvent evaporation technique

Emulsion solvent diffusion method:
In the emulsion solvent diffusion method, the medicine and organic solvent was a stronger affinity for each other than do the organic solvent and aqueous solvent. The drug absorbs in the organic solvent even though it is miscible with it, and the mixture is then dispersed in the water system to

produce the emulsion droplets. As the organic solvent gradually leaves the emulsion particles and reaches the surrounding aqueous phase, the aqueous phase diffuses into the particles in which the medication solidifies. [28]

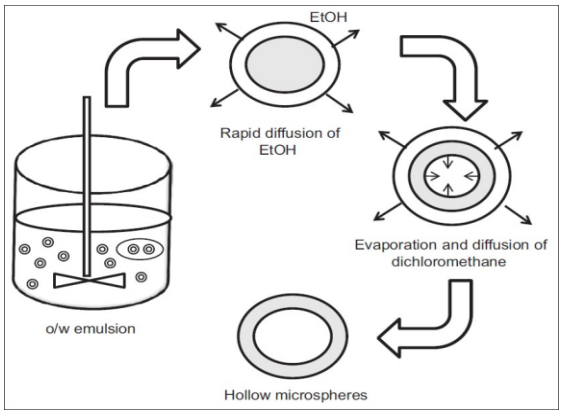

Fig.5: Emulsion-Solvent Diffusion Technique

Ionotropic gelation method:

Ionotropic gelation is a technique based on the ability of polyelectrolytes to cross link in the existence of counter ions to form beads. Since the development of alginates, gellan gum, chitosan, and CMC for the encapsulating of pharmaceuticals and even cells, ionotropic gelation technique was widely used for this aim. Natural polyelectrolytes include particular anions, but they also cover the drug core and operate as release rate decelerators. These anions predominantly connect to the anion blocks to create gelation and join with the polyvalent cations to form meshwork structures. Hydrogel beads are produced by mixing an aqueous solution with polyvalent cations with a drug-loaded polymeric solution. [29]

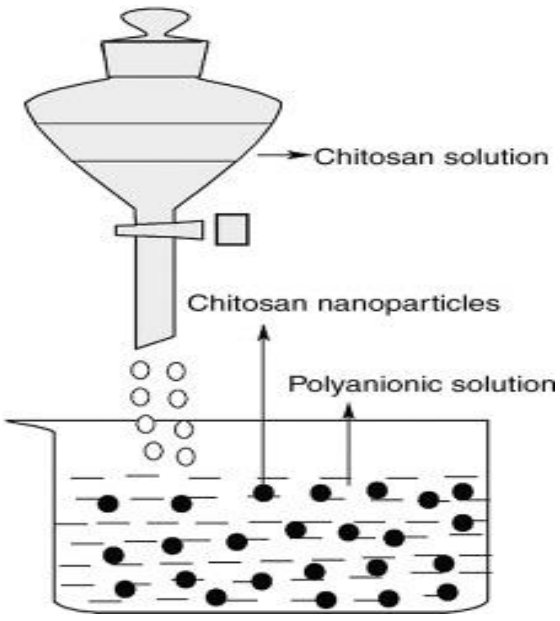

Fig.6: Ionotropic Gelation Method

EVALUATION OF MICROSPHERES

Micromeritic Properties:

The microspheres' micromeritic characteristics, including as particle size, tapped density, bulk density, compressibility index, and flow characteristics, were identified. The mean particle size was obtained by measuring 100 particles with the use of a calibrated ocular micrometre, and the size was assessed using an optical microscope. The following values for the tapped density, bulk density, and percent compressibility index were obtained using the bulk density apparatus: [30]

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

$$\text{Tapped Density} = \frac{\text{Weight of microspheres}}{\text{Volume of microspheres after tapping}}$$

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

Percentage Yield:

The formula below represents the percentage yield of floating microspheres, which is derived by dividing the actual product weight by the sum of all the non-volatile ingredients employed in their synthesis. [31,32]

Drug entrapment efficiency:

By immersing the weighted amounts of crushed microspheres in the necessary quantity of 0.1 N HCl and analysing spectrophotometrically at a certain wavelength utilizing the calibration curve, it is possible to estimate the amount of drug content in floating microspheres. Each batch should undergo a triplicate drug content analysis. Divide the real drug content by the hypothetical drug loading of the microspheres to determine the trapping effectiveness of floating microspheres. [33, 34]

Floating Behaviour:

100 ml of the simulated gastric fluid (SGF, pH 2.0) is added, along with the appropriate amount of the floating microparticles, and the mixture is mixed using a magnetic stirrer. After pipetting, the layer of buoyant micro-particulates is removed by filtering. The sinking particulate layer's particles are separated via filtration. In a desiccator, both types of particles are dried until they have a constant weight. Calculating buoyancy involves weighing both microsphere fractions and comparing the quantity of

the floating particles to the sum of the floating and sinking particles. [35]
Buoyancy (%) = Wf/ Wf + Ws

Invitro Release studies:
Using a basket-type dissolving equipment in accordance with United States Pharmacopoeia (USP) XXIII, the release rate of floating microspheres is assessed. A hard gelatin capsule (No. 0) is filled with a weighed quantity of floating microspheres equal to 50 mg of medication and put in the basket of the dissolving rate equipment. The dissolving media is 500 cc of the SGF with 0.02% w/v Tween 20. A rotational speed of 100 rpm keeps the dissolving fluid at 37 1 °. The drug release investigation was conducted under ideal sink circumstances. Every 30 minutes, 5ml samples are taken, put through a 0.25 m Millipore membrane filter, and then the concentration in the dissolving media is determined using the LC/MS/MS technique. After each withdrawal, 5 ml of new dissolution fluid is added to maintain the dissolution fluid's starting volume.

In-vivo Studies:
X-ray images of barium sulphate-loaded hollow micro-particulates in beagle dogs' stomachs can be used to study the in-vivo floating behaviour. In a dissolving test using a dissolution medium, the in-vitro drug release investigations are carried out. The investigation can be carried out using the appropriate animal models to get the in-vivo plasma profile. [30, 36, 37].

CONCLUSION

There are many different ways that a medication can be digested in the digestive system, and the longer the dose form is kept in the stomach, the longer it will take for the medication to be assimilated. The hollow microsphere has promise as a possible strategy for gastric retention. Although there are a lot of challenges to overcome in order to achieve extended gastric retention, several businesses are working to commercialise this method.

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