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A REVIEW ON HALLOW MICROSPHERES – A NOVEL DRUG DELIVERY SYSTEM

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Abstract
In order to accomplish stomach retention, the author of this review on hollow microspheres gathered the most recent research, paying particular attention to the main flotation process. One strategy is to create hallow microspheres that will prolong the stomach absorption period.The bioavailability of medications is predicted to be improved by floating drug delivery systems which are developed to stay buoyant on the gastriccontents used intended for an extended period of time. Hollow microspheres are spherical, empty, powders made of synthetic polymers that are free-flowing and, range in size from 1 to 1000micrometers. The in-vitro dissolution study to assess the functionality and uses of floating microspheres is also detailed in the present overview.

Keywords: Hallow Microspheres, Gastro Retention, Polymers.

INTRODUCTION

Because of its simplicity, patient compliance, and economics, the oral route of administration is the most generally accepted approach. But the main disadvantage of Because of the physiology and transit time involved in oral medication distribution, not all the drugs molecules are consistently absorbed during the gastro intestinal tract along with leading to inadequate bioavailability and non-reproducible therapeutic effects. So, a subgroup of control release systems known as gastro-retentive drug delivery systems is created. These free-flowing powders are composed of artificial polymers and are naturally decomposable usually produced by mixing in drugs with controlled release potential across the matrix.[1,2]

Gastro Retentive Drug Delivery System

One useful technique for ensuring a longer and more consistent drug delivery in the GIT and controlling gastrointestinal residence time is the use of GRDDS. The controlled retention of dose forms in the stomach is regulated through the use of flotation, mucoadhesion, expansion, and sedimentation. Based on this requirement, a variety of tactics to keep the dose form in the stomach have been suggested.[3,4]

METHODS OF GASTRIC RETENTION: The several methods utilised to lengthen a dose form's gastric retention time in the stomach include:

- Expandable and swelling system;

- Mucoadhesive or bio-adhesive system.
- Magnetic device.
- Ion-exchange resin.
- Super porous hydrogels and floating medication delivery systems are two examples.
- System with high density. [5]

FLOATING SYSTEMS

Low density, hydro-dynamically controlled devices with adequate buoyancy to propose above the stomach's inside for a long time are referred to as floating medication delivery devices. Increased stomach retention duration and fewer changes in plasma drug concentration arise from the medication's delayed, controlled release from the systems. [6]

CATAGORIES OF FLOATING DRUG DELIVERY SYSTEM

They are often divided into binary categories:

1. Effervescent system: It is a matrix-like structure that was produced by combining swellable polymers like methyl cellulose and chitosan with effervescent chemicals like citric acid and tartaric acid. In order to provide the dosage forms buoyancy, they are made in a way that Hydrocolloids that swell produce carbon dioxide when they come into touch with the acidic stomach contents. These are further separated into the two classes listed below:

2. Gas Generating System: Typically, these systems are made using resin beads that have been coated with ethyl cellulose and filled with bicarbonate. The coating is porous but impermeable, allowing water to pass through. The beads float in the stomach as a result of the carbon dioxide being released. [7]

3. Volatile Liquid Containing Systems: By incorporating an inflatable chamber with ether and cyclopentane, which gasifier at body temperature and causes the chamber in the stomach to fill, the gastric retension time of a drug delivery system can be maintained. [8]The volatile liquids are used to further broken down into the following three categories: Inflatable gastrointestinal medication delivery device; floating intragastric drug delivery system; and osmotically regulated intragastric drug delivery system.

B) Non-effervescent system: After swallowing in this of system expands from ingesting gastric fluid to the point where it inhibits them from passing through the stomach. This system is known as a "plug type system" because of its propensity to stay trapped close to the pyloric sphincter. The following are the several kinds of this scheme:

• Floating tablets with a single layer.
• Tablets with a bilayer that float.
• Compartment systems with microporous.
• Barrier system made of colloidal gel.

HALLOW MICROSPHERES

Hollow microspheres are spherical, empty particles without a core, according to a strict definition. These low density systems are long-lasting in the stomach and buoyant enough to float over gastric contents. They have a high surface to volume ratio as a result of their small size. They are made to float on stomach fluid that is less dense than one due to this characteristic, stomach transit is slowed. As the medication is delivered gradually and at the right pace, there are less changes in the drug's plasma concentration, which leads to improved stomach retention. [9]

Advantages of Hallow Microspheres[10]

1. Because changes in plasma drug conc. are minimized and continuous drug release is sustained, bioavailability improves despite first pass metabolism.
2. Improves the absorption of medications that can only be dissolved in the gastrointestinal.
3. Drugs with a short half-life can provide therapeutic effects.
4. Increase the selectivity of receptor activation.
5. Minimized adverse activity at the colon.
6. Increases cooperation from the patient by reducing dose frequency.
7. Flexibility in the design of the dose form is noted.
8. Specific treatment for indigenous conditions in the upper GIT
9. The pharmacological effects and clinical results of sustained mode of drug release are enhanced by extending the period over a critical concentration.

Mechanism of Flotation[2,12]

The medication floats on the contents of the stomach and is gradually removed from the body at the correct rate. Once the medication has been discharged, the remaining system from the stomach is emptied. However, a limited amount of floating force is also required to keep the dose form constantly buoyant on the surface of the meal, in addition to the minimal stomach content required to allow the optimal accomplishment of the buoyancy retention principle.

When the hollow microspheres come into contact with stomach in gastric fluid, gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier. This barrier to control the rate of fluid penetration into the device and subsequent medicine release. The neighbouring hydrocolloid layer's hydration protects the gel layer from dissolving when the dosage form's outside surface does. The expanded polymer decreases density and provides the microspheres buoyancy by capturing air. However, a little stomach content is necessary for the best achievement of buoyancy.

Polymers used in hallow microspheres[13]

Polymers that are both biodegradable and non-biodegradable are utilised. Among the polymers utilised are:

1. Hydrophilic polymers: Ex: chitosan, gelatin, egg albumin, starch, and cellulose derivatives.

2. Hydrophobic polymers: Ex: Polylactic acid, ethyl cellulose, and acrylic acid esters.

3.Biodegradable polymers: These items may gradually vanish from the administrative site.Examples include polyglycolic acid (PGA), polycaprolactone (PCL), and polylactic acid (PLA).

4. Non-biodegradable polymers: These substances are still by nature and can be eradicated by removal since the position of administration since natural organisms are unable to break them down.For instance, polyethylene, polyether urethane (PEU), eudragit, and polyethylene vinyl acetate (EVA).

5. Soluble polymers: These are uncross-linked polymers with a modest molecular weight liquefy in water. Examples include polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), and Eudragit, a co-polymer of methacrylic and acrylic acids.

6. Hydrogels: When in contact with water, these polymers swell but do not disintegrate. These have been removed entirely from the administration site since they are inactive. They function by putting up a barrier that regulates the flow and release of medications at a particular rate.Examples include cross-linked polyvinyl alcohol (PVA), polyhydroxy ethyl methyl acrylate (PHEMA), polyvinyl pyrrolidine (PVP), and polyvinyl alcohol (PVA).

Methods of Preparation

1. Spay drying technique: Polymeric mixed microspheres containing the medication are created using this method. A volatile organic solvent is used to dissolve the polymer initially. After that, a high-speed homogenizer is used to spread the medication (in solid form) throughout the polymeric solution. [14]

2. Solvent evaporation: The medication is either dispersed throughout the polymer solution or dissolved inside it once the polymer has been dissolved in an organic solvent. The medicinal solution is first emulsified into an aqueous phase containing polyvinyl alcohol, and then it is transformed into an o/w emulsion. The organic solvent is evaporated when a stable emulsion has formed by either raising the temperature or stirring frequently. When the solvent is removed, the polymer precipitates at the droplets' o/w interface, giving them a cavity and hollow interior that permits them to float.[15]

3. Ionic gelation method: In this method, the polyelectrolyte forms beads by cross-linking with the opposing ions. Typically, encapsulating materials including alginates, chitosan, gellan gum, and carboxymethyl cellulose are utilised. These organic polyelectrolytes function as release rate retardants in addition to coating substances. These have specific anions on their structure, which combine with the polyvalent cations to generate a meshwork structure that causes gelation. The drug-polymer solution is combined with aqueous cation solution to create microspheres. A 3D ionically cross-linked moiety is finally created.[16-17]

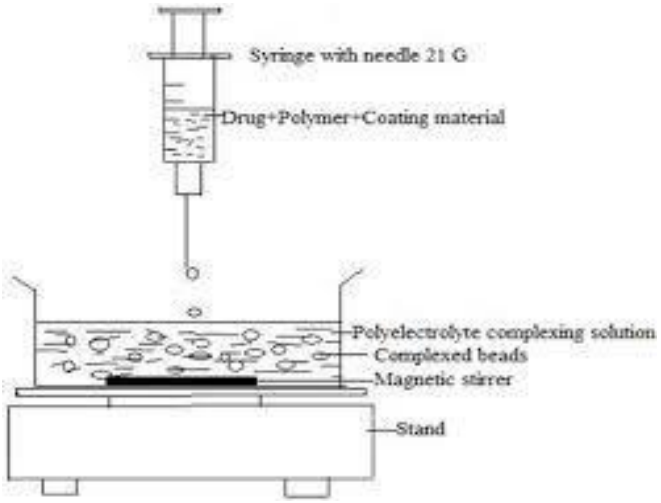

Fig.1: Ionotropic Gelation Method

4. Single emulsion technique: The natural polymers are spread in a non-aqueous liquid, such as oil, after being dissolved or dispersed in an aqueous medium. The scattered globule is then cross-linked in the following phase, which can be accomplished using either heat or chemical cross-linkers.[18]

5. Double emulsion technique: The production of numerous emulsions or the double emulsion type w/o/w is a step in the double emulsion method. The protein is included in the dispersed aqueous phase of the continuous phase made up of the polymer solution. After that, the primary emulsion undergoes homogenization, which causes a double emulsion to develop.[18,19]

6. Phase separation co-acervation technique: It is based on the co-acervation theory, which claims that the creation of a polymer-rich phase is caused by a reduction in the solubility of the polymer in the organic phase. In a system to additionally includes an incompatible polymer that

causes the first polymer to phase separate and engulf the drug particles, the drug particles are dissolved in a polymer solution.[20]

7. Emulsion solvent diffusion method: Despite the fact that the organic solvent is miscible, in this method the drug is dissolved in the organic solvent before the solution is spread throughout the aqueous solvent to form the emulsion droplets. As the organic solvent progressively moves out of the emulsion droplets and into the surrounding aqueous phase, it diffuses into the droplets where the drug crystallises.[21]

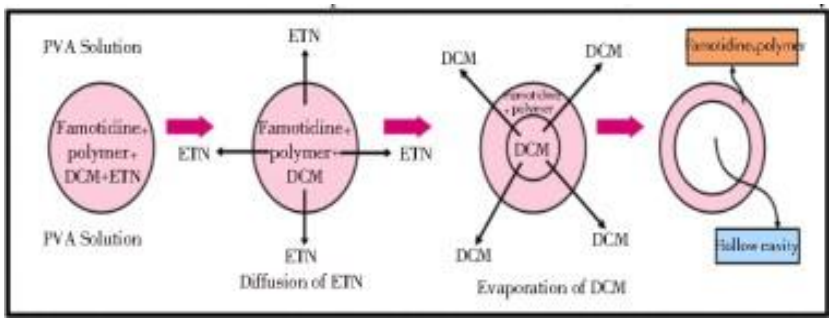

Fig.2:Emulsion solvent diffusion method

Evaluation of Hallow Microspheres

1. Micromeritics: They fall under the following categories:

A. Particle size: By means of an optical microscope, the microspheres' particle size was determined. Each batch's microspheres are counted by sifting them for 15 minutes in a motorised shaker.The hollow microspheres of the average particle size are used to calculate the particle size distribution. [22]The formula is as tracks:

Mean particle size = Σ (mean particle size of the fraction × weight fraction)/Σ (weight fraction).

B. Bulk density: The weight of a test sample divided by its volume is known as its bulk density. Find it by precisely weighing a 10 g sample before placing it in a 25 ml measuring cylinder. Without moving the cylinder, the bulk density is estimated using the equation (values stated in gm/cm3) by measuring the volume occupied by the granules.[23]

Bulk density = Weight of sample/Volume of sample

C. Tapped density: By dividing the microspheres' mass by their tapped volume, the tapped density may be compute it. The tapped density was calculated from the final volume using the following equation (values stated in gm/cm3).[23]

Tapped density =Mass of hallow microspheres/Volume of hallow microspheres after tapping

D. Hausner's ratio: The Hausner's ratio is a measure of a powder's compressibility.The Hausner's ratio greater than 1.25 is considered to have poor flowability .[23]

The formula is used to compute it:

Hausner's Ratio = (Tap density/Bulk density)x100

E. Carr's compressibility index: The flowability of a powder is determined by the Carr's index. The formula is used to compute it:

Carr's index(%) = (Tap density-Bulk density/ Tap density)X100

A powder with good flow properties has a value below 15%, whereas one with poor flow characteristics has a value above 25%.[23]

F. Angle of repose (θ): It's employed to figure out the flow property. The measuring is done with a funnel. Positioned 2.5 cm above the horizontal surface is the funnel's stem. When the funnel's tip was just over the pile's height, the sample powder was permitted to trickle out of it. By tracing a boundary around the pile's perimeter and averaging its three diameters, the diameter of the pile was calculated. .[23] The angle of repose is calculated using the formula below:

$\tan(\theta)=h/r$

Where,

θ is angle of repose

h is height of the pile

r is the radius of the pile.[23]

Table 1: Relationship between angle of repose and flowability

S.N.	Angle of Repose (degrees)	Flowability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

2. Drug entrapment efficiency (DEE): By crushed these hollow microspheres and separating with portions of 0.1N hydrogen chloride, the quantity of the drug trapped was calculated. A volumetric flask with a 100 ml capacity was filled with the extract, and the remaining space was filled with 0.1N HCl. A spectrophotometer was used to measure the absorbance vs. blank surface after the solution had been filtered. [24] The amount of drugs trapped in the hollow microspheres was calculated using the method below:

DEE= (amount of drug actually present/theoretical drug load expected)X100

4. Percentage yield: The percentage yield of buoyant microspheres was calculated by dividing the actual mass of the outcome by the sum of all non-volatile materials used to generate hollow microspheres. [24] The equation reads as follows:

Percentage yield=(actual weight of hallow microspheres/weight of total drug taken+total weight of polymer)X100

5. Percentage Buoyancy: Hollow microspheres will be dispersed in 900 ml of 0.1 N HCL (pH 1.2) field with a USP dissolving equipment type II surface. The medium is stirred for 12 hours with a paddle rotating at 50 rpm. The hollow microspheres will be weighed after drying. [25] The following are the % buoyancy calculations:

Buoyancy(%)= Wf /(Wf+Ws) X100

Where,

Wf and Ws are the masses of the floating and settled micro particles.

5. Dissolution test: Using a (USP) I basket type dissolving equipment, the in-vitro release rate of hollow microspheres was calculated. A hard gelatin capsule was filled with a known quantity of hollow microspheres equal to the medication dosage, and the capsule was then put in the dissolution rate equipment' basket. The dissolving media was employed, and 900 ml of it was agitated at 100

rpm at 37 +/- 0.5˚C. At certain intervals, samples are taken out and subjected to UV spectroscopic analysis. [23]

6. Swelling studies: In order to determine the molecular characteristics of swelled polymers, swelling investigations were carried out. With the aid of advanced techniques like optical microscopy and dissolving apparatus, swelling studies may be assessed. The following formula was used to compute the swelling studies using the Dissolution apparatus: [23]

Swelling studies = Weigh of weight formulation/Weight formulation

6. Stability studies: In these experiments, the formulation was packed tightly inside polyethylene-coated aluminium packaging. The samples were housed in the stability chamber for three months, which was maintained at 40 °C and 75% RH. At the end of the research, the samples' physical qualities and drug content were inspected. [26]

Applications of Hallow Microspheres:[27,28]

1. It is possible to employ hollow microspheres as carriers for medications with an absorption window. Suphonamides, tetracyclines, quinolones, cephalosporins, and other medications, for instance, can only be absorbed through particular regions of the GI mucosa.
2. One of the most effective ways to deliver drugs with low bioavailability is using hollow microspheres. Examples are riboflavin and furosemide..
3. They are useful for improving the absorption of partially and entirely insoluble medications.
4. In this strategy may be used to transport non-steroidal anti-inflammatory medicines (NSAIDs) for controlled release, which reduces the main adverse effect, stomach discomfort.
5. Hollow microspheres enhance stomach pharmacotherapy by allowing for local medication release. Through this, the mucosa's medication concentration rises, which is beneficial for treating H.pylori infections.
6. Site-specific targeting, which enables the avoidance of drugs with accelerated first pass metabolism and guarantees that only the stomach or proximal small intestine may absorb the medication, is another important feature of hollow microspheres. A few drugs that are absorbed from the stomach or the early part of the small intestine such as riboflavin, furosemide, and misoprostol.
7. To create sustained release dosage forms that release the medicine over a longer period of time the hollow microspheres are employed.The gastric residence time (GRT) is lengthened as a result.

Table 2: Marketed Products of Floating Drug Delivery Systems

S.NO	Brand name	Delivery system	Generic name	Daily dose	Company name
1	Madopar® HBS	Floating CR Capsule	Benzerazide(50mg, Levodopa(200mg)	Benzerazide(150mg), Levodopa(600mg)	Roche Products, USA
2	Valrelease®	Floating capsule	Diazepam (15 mg)	30mg	Hoffmann-LaRoche, USA
3	Cytotec®	Bilayer floating capsule	Misoprostal (100 mcg/200 mcg)	400/800mcg	Pharmacia, USA
4	Cifran OD®	Gas generating floating tablet	Ciprofloxacin(1gm)	1 g	Ranbaxy, India
5	Oflin OD®	Gas generating floating tablet	Ofloxacin (400mg)	800mg	Ranbaxy, India

CONCLUSION

The rate at which a drug is absorbed in the gastro intestinal tract (GIT) are varies greatly, and it takes longer for a drug to be absorbed the longer the dose form is kept in the stomach.The hollow

microsphere has promise as a possible strategy for gastric retention.Numerous businesses are working to commercialize this approach, despite the fact that there are still a number of challenges to be overcome in order to achieve prolonged gastric retention. These pharmaceutical approaches to distribution promoting the development of innovative, controlled, and formulations for prolonged gastrointestinal release,improvement of pharmaceutical research and development.

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