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A Review on - Formulation and Evaluation of Gastroretentive Microballoons for Sustained Drug Delivery

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ABSTRACT

Gastroretentive dosage form are an approach for prolonged & predictable drug delivery to control in the upper GIT to control the gastric residence time. One promising method for gastric retention appears to be the use of microballoons. Drug delivery methods using microballoons based on non-effervescent system with empty, spherically shaped particle without cores, ideally less than 200 micrometer. Microballoons are controlled release medication delivery devices with gastroretentive qualities. The benefits, drawbacks, preparationmethods, applications, polymers utilizedin microballoons, characterization & formulation, aspects with different assessment methodologies and commercialized products are all thoroughly explored.

Keywords: Microballoons, Gastroretentive, Gastric time, Gastric emptying, Buoyancy

INTRODUCTION

The real challenge in the development of controlled drug delivery system is not just to sustain the drug release but also to pr olong the release of drug over an extended period of time. The oral route is considered as the most promising route of drug delivery.(2)In order to control the gastric residence duration, prolonged gastric retention is necessary since it keeps the stomach's controlled release system functioning as intended for a longer period of time. Low-density systems, such as hydrodynamically controlled systems that float, are less dense than gastric fluid. These systems are sufficiently buoyant to float above the contents of the stomach and stay buoyant there for an extended amount of time without slowing down the rate at which the stomach empties.The medicine is released from the formulation gradually and at the desired pace while it is floating on the stomach contents.(4)

Gastroretentive Drug delivery systems (GRDDS)

Gastroretentive drug delivery systems are dosage formulations that have a longer half-life in the stomach (GRDDS).
These medications benefit from GRDDS since they increase the drugs absolute bioavailability, therapeutic effectiveness, gastric residence time (GRT), potential dose reduction, decrease drug waste, and increase the solubility of medications that are less soluble in high pH environments.(34)

Floating drug delivery system

Davis gave a description of a floating medicine delivery device (1968).(34) These systems are low-density based and have enough buoyancy to float over the contents of the stomach. The medication is gradually discharged from the system at a steady rate while it is floating on the stomach contents. The drug's residual system is removed from the stomach once it has

Been released. This raises GRT, lowers medication variation, and improves absorption. On the basis of grains, powders, capsules, tablets, laminated films, beads, and hollow microspheres, numerous floating systems have been developed. [35,36] It can be classified into two systems: [11,12]

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)

Non-Effervescent Systems
Hydro colloidal gel barrier systems
Micro porous compartment system
Alginate and pectin beads

Microballoons
Microballoons are non-effervescent medication delivery methods that are gastrointestinal retentive. Microballoons 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.[1]

Microballoons loaded with drugs in their outer polymer shell were prepared by simple solvent evaporation or solvent diffusion evaporation method to prolong the GRT of the dosage form. The microballoons floated continuously over the surface of an acidic dissolution media containing a surfactant for more than 12 hours.[5]

Solvent evaporation or solvent diffusion/evaporation are two innovative technologies used to construct a hollow inner core of microballoons loaded with medicine in their outer polymer shell. The medication and a mixture of enteric acrylic polymers are dissolved in an ethanol/dichloromethane solution and then added to an agitated Poly Vinyl Alcohol (PVA) solution that is heated to 40 ºC. Once a stable emulsion has formed, the organic solvent is removed from the emulsion by stirring continuously or by raising the temperature while applying pressure. Dichloromethane evaporation creates the gas phase in the droplet of dispersed polymer, creating the hollow interior cavity in the polymer microsphere containing the medication. For nearly 12 hours, the microballoon remains suspended above the surface of an acidic dissolving medium that contains surfactant.[6]

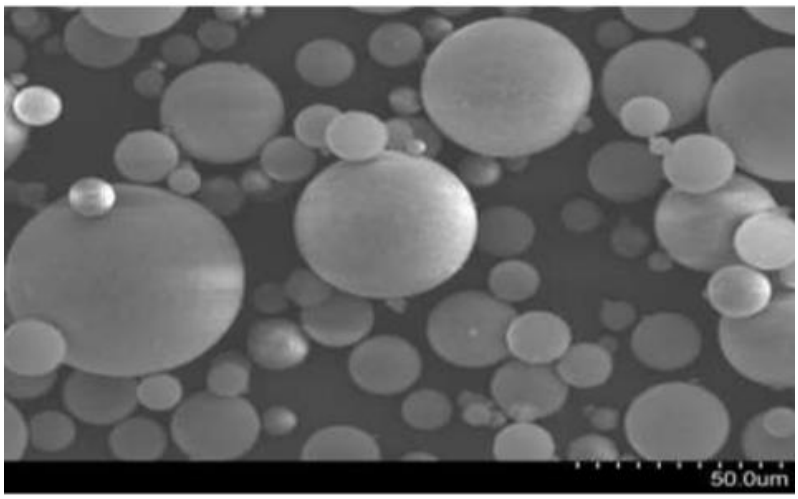

Fig 1: Microballoons

Applications of Microballoons
- Through local drug release, microballoons can improve stomach pharmacotherapy and result in high drug concentrations in the gastric mucosa. This eliminates Helicobacter pylori from the stomach's submucosal tissue and enables the treatment of gastritis, esophagitis, stomach and duodenal ulcers.
- These microballoons facilitate long-term drug release and allow for sustained drug release behavior. To create a floating, controlled drug delivery system, microballoons are created.
- According to a recent description, some medications, such as prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride, Riboflavin, Aspirin, Griseofulvin, Ibuprofen, and Terfenadine, can be encapsulated in microballoons to lessen variations.[6,7,10]

- Absolute bioavailability can be improved by using microballoons to significantly increase the absorption of medications with low bioavailability.
- Drug administration by microballoons is site-specific, particularly for medications that are specifically absorbed from the stomach or the proximal portion of the small intestine.

Advantages

- Enhances patient compliance by lowering the frequency of dose.
- Increased drug usage will increase bioavailability, decrease the frequency or severity of side effects, and, despite the first-pass pass effect, prevent fluctuations in plasma drug concentration, allowing for continuous drug release to maintain a desired plasma drug concentration.[8]
- Because of their buoyancy, microballoons lengthen the gastric retention period while reducing material density. [9]
- Improved absorption of medications that only dissolve in the stomach.[9]
- Controlled drug releases over an extended duration.
- It is possible to administer medication to the stomach at a specific site.
- Superior than single-unit floating dosage forms because the medicine is released evenly by these microballoons and there is no risk of dose dumping.
- Preventing stomach discomfort due to the prolonged release effect. Better therapeutic effect of short halflife drugs can be achieved.[11,12]
- Microsballoons morphology allows a controllable variability in degradation and drug release.[13]

Disadvantages

- There are several elements that can affect the controlled release dosage form's release rate, including the food and the speed at which it passes through the stomach.
- Differences in the release rate between dosages.
- The modified release from the formulations.
- Because controlled-release formulations often have a higher drug load, any compromise to the dosage form's release properties could potentially be hazardous.[13]

Mechanisms of Microballoons

Microballoons are low-density devices with enough buoyancy to float over gastric fluid and stay there for extended periods of time. The medication is given gradually at the appropriate rate as the device hovers over the gastric fluid, increasing gastric retention and minimizing variations in plasma drug concentration. The gel that forms and the polymers that hydrate to form a colloidal gel barrier that limits the pace of fluid penetration into the device and the subsequent release of medication occurs when stomach fluid comes into contact with microballoons. The hydration of the nearby hydrocolloid layer preserves the gel layer when the dosage form's outer surface dissolves. The swollen polymer traps air, causing its density to drop below that of the stomach fluid and giving the microspheres buoyancy. However, a minimum gastric content is required to enable appropriate buoyancy accomplishment. [14,15]

Materials

Drug

Drugs having a limited therapeutic window in the GI tract, mostly absorbed from the stomach and upper portion of the GIT, acts locally in the stomach, breaks down in the colon, and alters the natural flora in the colon.

Polymers

Cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene. [10,16,17]

Solvents

It must to possess good volatile characteristics, enabling it to effortlessly separate from the emulsion and leave behind hollow microspheres.[18]

Surfactant

Tween 80, span 80 and SLS

Hardening agent

N-hexane, petroleum ether.

Method of preparation

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 whattman filter paper. This hollow microspheres imparts the floating and sustained properties.[19](Fig 2).

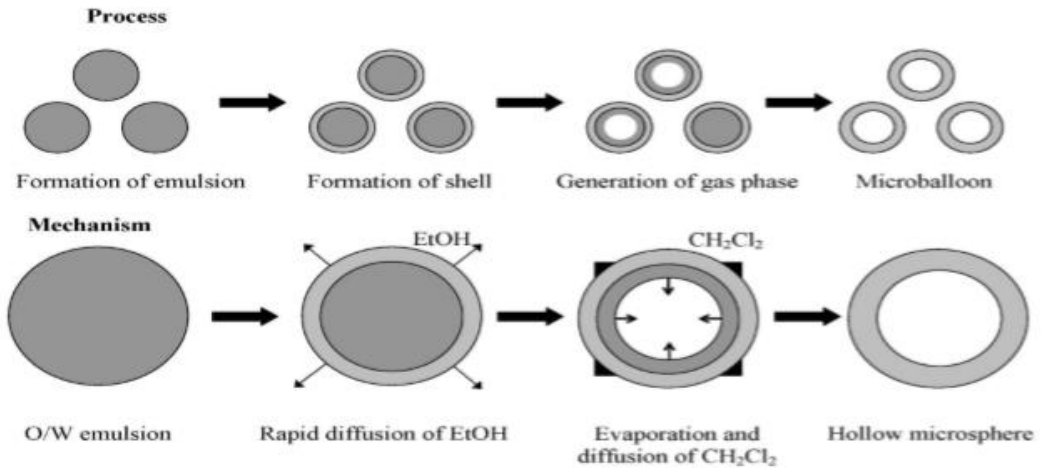

Fig 2: Solvent evaporation method

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 mixture is stirred for an hour at 1500 rpm and various temperatures.

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. Despite the organic solvent's miscibility, the medication dissolves in it and the mixture is then distributed throughout the aqueous solvent to form the emulsion droplets. 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. [19,20] (Fig 3).

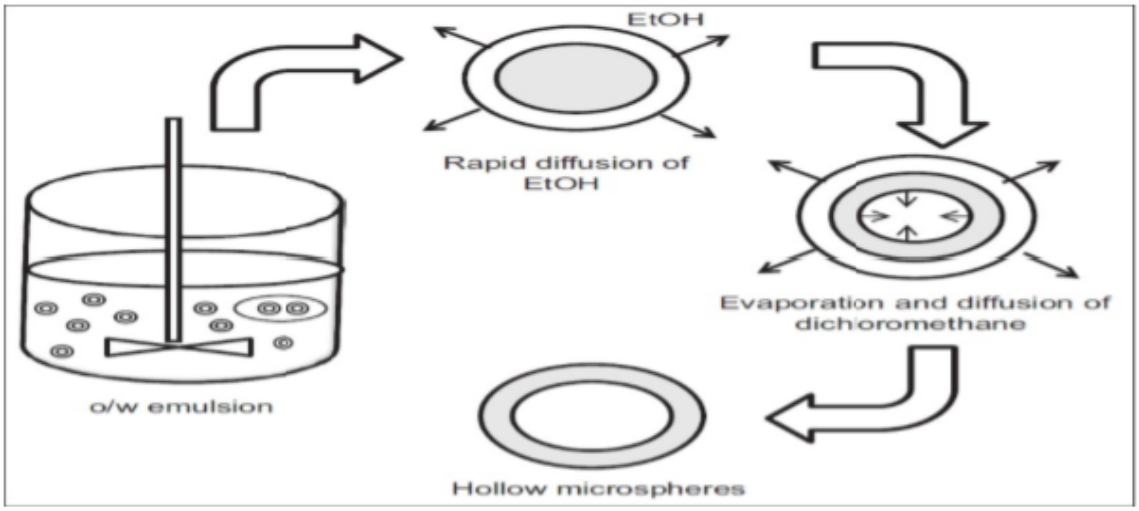

Fig 3: Emulsion solvent diffusion method

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/w of polyvinyl alcohol as emulsifier. This is stirredusing propeller agitator for 1 hour for evaporation of organic solution and then filtered it.[21] The bestformulation is selected on the basis of optimized result of various process variables such as polymer ratio, drug: polymer ratio, stirring speed and concentration of emulsifier.[21].

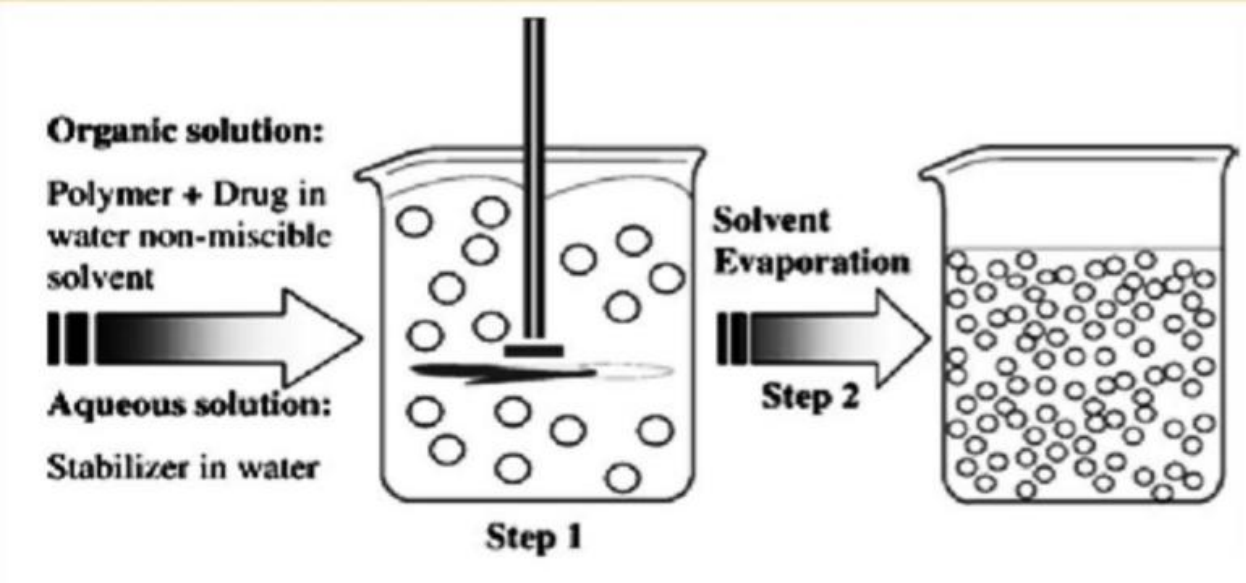

Fig. 4: Solvent diffusion-evaporation technique

4) Spray drying

The most used industrial method for drying and forming particles is spray drying. When the necessary particle size distribution, bulk density, and particle shape can be achieved in a single step, this procedure is optimal. [22]

To create a slurry, the polymer is first dissolved in an appropriate volatile organic solvent, such as acetone, dichloromethane, etc. Following the slurry's spraying into the drying chamber, a concentration gradient of the solute forms inside the tiny droplet, with the droplet surface exhibiting the highest concentration. This is due to the fact that the solute takes longer to diffuse than the solvent in the droplets to evaporate during drying. A solid shell then forms, which facilitates the creation of microspheres. A cyclone separator is typically used to separate the solid products from the gases, and the products are vacuum-dried to eliminate any remaining solvent before being stored for future use. [23]

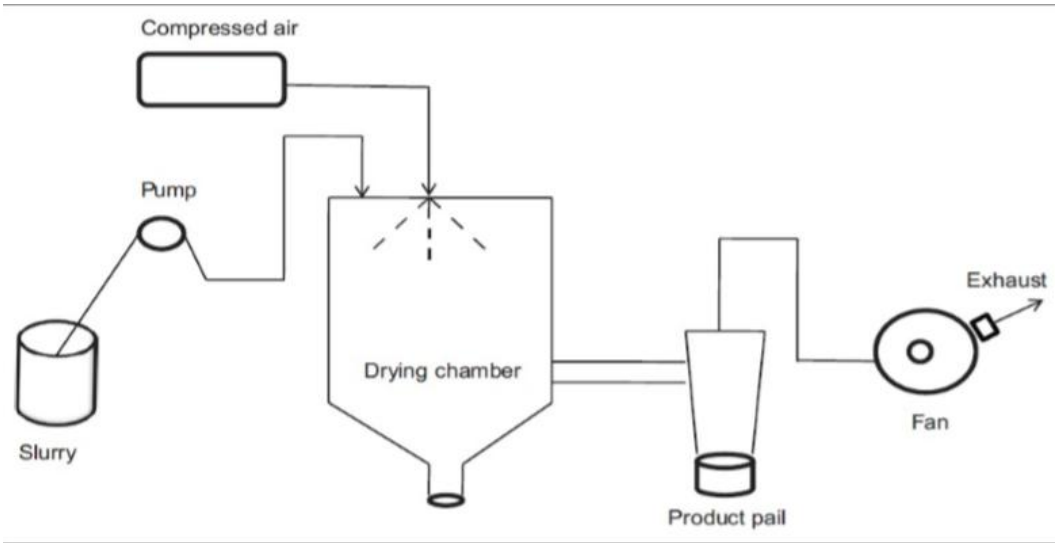

Fig. 5: Spray drying method

Evaluation of microballoons

i. Percentage Yield

The percentage yield of the hollow microspheres is determined for drug and is calculated using the following equation.[24,25,26]

Yield=M/Mo x 100

Where M = weight of beads

Mo = weight combined of the drug and polymer.

ii. Micromeritic properties [27, 28]

The micromeritic qualities of microballoons are assessed based on their size and shape, bulk density, tapped density, Hausner's ratio, and flow characteristics, which are established by the carr's index and angle of repose. [27]Optical microscopy is used to measure particle size, and a calibrated ocular micrometer is used to calculate the average diameter of the particle.(by measuring 200 to 300 particles).[28]The liquid displacement method yields the true density; the fixed funnel method yields the angle of repose; and the bulk density device yields the tapped density and compressibility index by measuring the volume change. Scanning electron microscopy confirms that microspheres are hollow.

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

$$I = Vb - Vt / Vb \times 100$$

Where, Vb is the bulk volume and Vt 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. A helium densitometer is used to measure true density. Equation for calculating porosity (e) is as follows:

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

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

iii. In vitro buoyancy

A suitable amount of empty or hollow microspheres is added to 900 milliliters of 0.1N HCl. For eight to ten hours, the mixture is agitated at 100 rpm in the dissolving device. The layers of buoyant microspheres are pipetted and filtered after 8 to 10 hours. Filtration separates the particles that are in the sinking particulate layer. Both buoyant and settled microsphere particles are dried in a desiccator until a consistent weight is reached. The weight ratio of floating microspheres to the total of floating and sinking microspheres determines in vitro buoyancy. Both the fractions of empty and hollow microspheres are weighed.[29,30]

$$\text{Buoyancy (\%)} = \{Wf / (Wf + Ws)\} \times 100$$

Where, Wf = weights of the floatingmicrospheres and

Ws=weights of thesettled microspheres

iv. Scanning electron microscopy

Dry hollow microspheres are coated with gold using an ion sputter and mounted on a brass stub used in electron microscopy. Next, spectro random scanning of the stub is used to capture images of the microsphere. Viewing the microspheres at a 20 KV accelerating voltage. [31]

v. 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 measured quantity of hollow microspheres, packed into a hard gelatin capsule, equal to the prescribed Dosage of the medication, is placed in the dissolution rate equipment basket with the dissolving medium inside. The rotation speed is set at a certain rpm, and the dissolving fluid is kept at 37 ± 1 °C. The drug release investigation is conducted under ideal sink circumstances. A small volume (5 ml) of samples is taken out at each time interval, and the concentration of microballoons in the dissolving medium is measured using the liquid chromatography/mass spectroscopy method. After each withdrawal, 5 ml of new dissolution fluid is added to maintain the original volume of the dissolving fluid. Every experiment is conducted three times.[32]

vi. Swelling studies

The molecular characteristics of swelled polymers are calculated by swelling studies. 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) lab India disso 2000) is calculated as per the following formula. [33]

Swelling ratio = Weight of wet formulation / Weight of formulations

CONCLUSION

According to a recent assessment, the floating microballoons demonstrated a controlled release delivery system that is retentive, suggesting that this could be a viable method for gastric retention.

Microballoons have a low density and enough buoyancy to float above the gastric content and stay there for an extended amount of time. As the medication floats over the stomach contents, it releases gradually at the prescribed rate, reducing variations in the plasma drug concentration.

It is a productive way to increase the bioavailability. Optimized microballoons will play a key role in innovative medication delivery, specifically in the areas of diagnostics, gene & genetic materials, safe, targeted, and efficient in vivo distribution, as well as the sorting of diseased cells.

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