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Review Article

Floating Microsphere: A Review on Novel Approach

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Abstract

Microspheres that float around on the surface are also known as micro-balloons, floating microparticles, or hollow microspheres. Floating microspheres, according to strict definition, are spherical, centerless particles. Particles of diameters ranging from 1 to 1000 µm are these free-moving things. Floating microspheres are gaining a lot of interest because they have the potential to deliver drugs directly to the stomach. One type of non-effervescent drug delivery device that is gastrointestinal retained is the hollow microsphere, which is also called a floating microsphere. Hollow microspheres are spherical, coreless particles that are ideally between one and one thousand micrometers in size and composed of free-flowing powders of synthetic polymers or proteins. Medications that have an upper small intestine absorption window can benefit greatly from a controlled drug delivery system that has an extended stomach residence duration. Floating microspheres, sometimes called hollow microspheres, are gastro-retentive drug delivery devices that are based on the non-effervescent technique. Strictly speaking, hollow microspheres are spherical, coreless particles that are ideally between one and one thousand micrometers in size and formed of free-flowing powders of synthetic polymers or proteins. Floating microspheres that are able to retain their contents in the stomach for a long period are called gastro-retentive systems because of their low density and buoyancy. Fewer fluctuations in plasma drug concentration and increased stomach retention result from medicine administration at the prescribed pace. To make microspheres that float, scientists use evaporation and solvent diffusion.

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Introduction

Thanks to new, easier-to-administer dosage forms made possible by cutting-edge drug delivery methods, the safety and effectiveness of therapeutic molecules have been greatly enhanced. A high rate of patient compliance has been seen while employing oral dosage forms due to their ease of handling and administration. Oral controlled drug administration aims to increase drug bioavailability and release from the system in a way that is easy to give, predictable and repeatable, and therapeutically effective—all while being simple and requiring little patient compliance. Another option is to enhance the drug's bioavailability in order to boost its therapeutic efficacy [1, 2, 3]. Longer dosing intervals and better patient compliance are two additional benefits of gastro-retentive dosage forms, which considerably increase the medicine's potential release duration. Floating ion exchange resins, raft-forming systems, expansion systems, high density systems, magnetic systems, mucoadhesive or bio-adhesion systems, low density systems, and super porous hydrogels are among the methods that can be employed to achieve gastric retention. equipment that transports medications on water. [2]

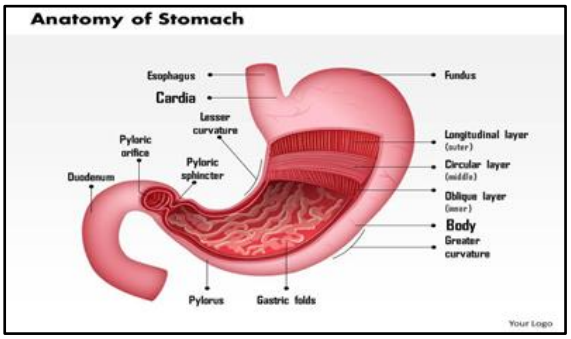

Fig.1 Anatomy of stomach

Floating microspheres, according to strict definition, are spherical, centerless particles. Particles of diameters ranging from 1 to 1000 µl are these free-moving things. Hollow microspheres, micro balloons, and floating microparticles are some of the names given to floating microspheres. Microspheres made of non-effervescent hollow polycarbonate were synthesized using an emulsion solvent evaporation technique. The idea behind this GI transit product is to let it float on gastric. [4]

Floating Drug Delivery System

System types that have a low density and sufficient buoyancy to float above the stomach contents for a long period are called floating systems. By keeping the device hovering over the stomach contents, the medication is given slowly and accurately, extending the gastro retention period and reducing changes in plasma drug concentration. [5]

Types Of Floating Drug Delivery System:

This system can be divided into two types:

1. Effervescent systems
2. non-effervescent systems

Effervescent Systems

Volatile liquid containing systems

An inflatable chamber filled with a gasifying liquid, like cyclopentane or ether, can be used to maintain the gastric reflux temperature (GRT) of a medication delivery system. This allows the stomach chamber to expand at body temperature. A biodegradable plug constructed of polyethylene, polyvinyl alcohol (PVA), or any other biodegradable substance could also be an alternative for the device. The stomach would be able to naturally expel the inflatable devices when they degrade because the chamber would release gas and collapse. [6]

Gas-generating Systems

Buoyant distribution methods lower the specific gravity of the system and make it float over water by releasing carbon dioxide through the effervescent reactions of citric/tartaric acid and carbonate/bicarbonate salts. This process is repeated in several systems [9, 12]. Sodium bicarbonate, citric acid, swellable polymers and polysaccharides (such as chitosan) are some of the possible components of these buoyant systems. [7]

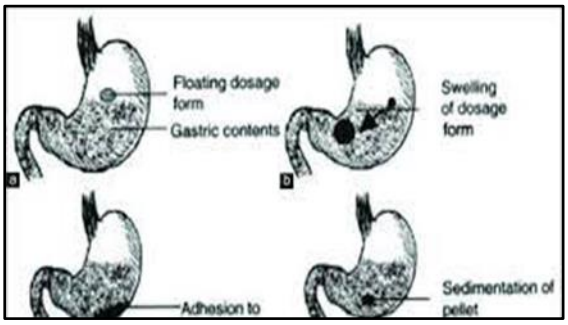

Fig. 2 Floating Behaviour of drug in stomach

in addition to containers containing a liquid that expands at room temperature or tartaric acid. [8]

Non-Effervescent Systems

One name for these systems is "plug type systems" due to their tendency to remain stuck around the pyloric sphincter. One method for making these dosage forms is to mix the drug with a gel. When taken orally, the gel expands in reaction to gastric juice while maintaining its shape and bulk density below one within the outer gelatinous cover. Because this kind of system absorbs gastric juice, it swells uncontrollably after swallowing, preventing the stomach from emptying. The expanded polymer gives these dosage forms their buoyancy. [9]

Colloidal gel barrier systems

These dosage forms float because the expanded polymer captures air with a density less than one. Originally proposed in 1975 by Sheth and Tossounian, the hydrodynamically balanced system (HBS). In these systems, hydrocolloids surround the medications, enabling them to float atop the contents of the stomach. Hydrocolloids (a gel-forming, highly swellable kind of cellulose), polysaccharides (in tablet or capsule form), and matrix-forming polymers make up the majority of the system (polyacrylates, polystyrene, HEC, HPMC, Nam). The hydrocolloid in the system hydrates when it comes into contact with gastric fluid, forming a colloidal gel barrier surrounding its surface. [10]

Approaches To Gastric Retention:

Several methods based on various principles can be employed to prolong the amount of time a dosage form stays in the stomach, a property known as gastric retention time (GRT). [9]

Floating Systems

Certain systems have a low density and can float for an extended period over the contents of the stomach. A longer gastro-retention period and less volatility in plasma drug concentration are achieved by gently administering the medication at the desired rate while the gadget hovers over the stomach contents. [11]

High density systems

These systems are held in place by the stomach rugae, which have a density of around 3 g/cm3. The peristaltic waves in the stomach won't harm them. Systems with a density threshold of 2.6-2.8 g/cm3 can be safely stored in the lower sections of the stomach. Coated pellets are used in formulations with a high density. Coatings are made with heavy inert minerals such as iron powder, zinc oxide,

titanium dioxide, barium sulphate, and others. [12]

Bio/Muco-adhesive Systems

The bio/muco-adhesive system can increase the drug delivery system's gastric residence time by making the medication's interaction with the biological membrane closer and longer. Their target is the mucin or stomach epithelial cells, where they cling. Binding of the two kinds of polymers to mucin and epithelial interfaces [13]

Swelling and Expanding Systems

The pylorus is unable to release these dosage forms due to their excessive inflation after swallowing. As a result, the dosage form remains in the stomach for a considerable duration. Given their propensity to stay lodged at the pyloric sphincter, these systems may be referred to as "plug type systems." [13]

Incorporation of passage delaying food agents5

Excipients used in food, such as fatty acids (such as myristic acid salts), alter the stomach's shape to mimic a fed condition, which in turn slows gastric emptying and allows for a significant delay in release.[14]

Development of Floating Microspheres

Medications dissolved or distributed within a particle matrix of solid biodegradable microspheres provide an opportunity for regulated drug release. Floating microspheres that are engineered to cling to the stomach contents for an extended duration are known as gastro-retentive microspheres. Hovering over the stomach contents allows for the precise and slow delivery of medication, which increases gastric retention with little changes to plasma drug concentration. The non-effervescent drug delivery method known as floating microspheres is gastro-retentive. Miniature spherical particles devoid of a core structure are known as hollow microspheres. With a dimension of little over 200 micrometers, these microspheres are free-flowing powders made of synthetic polymers or proteins. [15]

Mechanism of Flotation of Microspheres

The hydrocolloid layer next to the dosage form keeps the gel layer intact when the outer surface dissolves. Because the inflated polymer traps air, the density drops and the microspheres become buoyant. The correct attainment of buoyancy, however, requires only a small amount of stomach content. Microspheres can regulate the rate of medication release in response to stomach fluid contact by forming a colloidal gel barrier with the help of gel formers, polysaccharides, and polymers. [15]

Mechanism of drug release from the microspheres

Multiple pathways exist for the release of drugs from multiarticulate.

Diffusion

When particles come into touch with water-based gastrointestinal fluids, water diffuses into their interior (GIT). The medication is dissolved and then spreads outward through the release coat. [16]

Erosion

Some coatings can be engineered to dissolve slowly, releasing the drug contained within the particle. [16]

Osmosis

Osmotic pressure can be generated within a particle by letting water in, provided that certain requirements are met. Medication is expelled from the particle and onto the outside through the coating. [16]

Advantages of Floating Microspheres [17]

- Conditions specific to the upper gastrointestinal system can be treated more precisely.
- There has been a decrease in the variation of drug concentration.
- Receptor activation selectivity has been enhanced.
- There is less physical resistance.
- Concentration that is both important and effective for long periods of time.
- This enhances the bioavailability.
- Biotransformation in the first pass is enhanced.
- Medication delivery with reduced dose frequency and sustained effects.
- Minimized unfavourable action at the colon.

Disadvantages of Floating Microspheres [18]

- It would not be optimal to use medications like nifedipine, which is absorbed well throughout the gastrointestinal tract and undergoes first pass metabolism.
- Medications that aggravate the mucosa lining of the stomach should also not be administered.
- It is not advisable to incorporate drug compounds into the systems that are not stable in the acidic environment of the stomach.
- There must be a lot of stomach fluid for these medicine delivery devices to work correctly.
- Medications that have problems with GIT solubility or stability should not be used.
- Take the dosage form with a full glass of water (200-250 ml).

Method of Preparation of Floating Microspheres

There are multiple methods that can be used to prepare gastro-retentive floating microspheres. However, a large number of researchers throughout the world have extensively used the solvent evaporation method and the ionotropic gelation method to study floating microspheres from various angles. To successfully trap active components and create floating controlled release microspheres, the ideal approach must be selected. The choice of production technique is influenced by the drug, the composition of the polymer, and the intended use. [25]

Elements of process engineering and material properties have a significant impact on microsphere characteristics and the regulated release rate that follows. [19]

- Evaporation of a Spray-Dried Solvent
- An approach to gelation based on ions
- Method utilizing a single emulsion
- The method of double emulsion
- The co-acervation method for phase separation
- Wet spraying and wet spraying with a spray
- Transport of solvents in a quasi-emulsion

Spray Drying

It is necessary to dissolve the polymer in an appropriate volatile organic solvent before spray-drying it. The next step is to homogenize the solid medication with the polymer solution at high speed. The next step is to use a hot air stream to atomize the dispersion. When a solvent evaporates quickly, it forms little droplets or fine mists, which can then be further reduced in size to microspheres, which can range in size from 1 to 100 µl. [20]

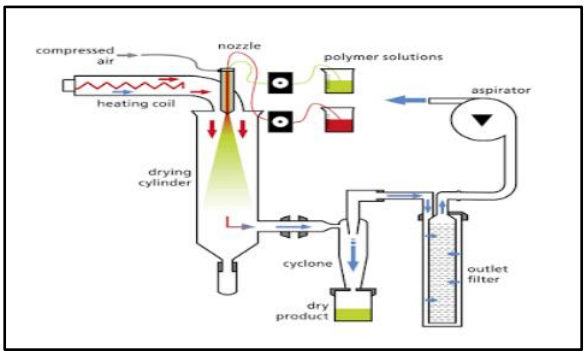

Fig. 3 Spray drying

Solvent Evaporation

After the liquid production vehicle phase is completed, the solvent evaporation process is complete. A non-soluble volatile solvent is added to the liquid production vehicle phase to distribute the microcapsule coating. A microencapsulating core material is dispersed or dissolved in the coated polymer solution. The liquid production vehicle phase is used to agitatedly distribute the core material combination in order to generate the microcapsules of the correct size. [21]

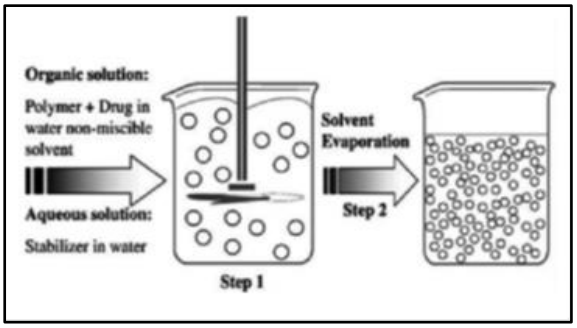

Fig.4 Solvent Evaporation method

Ionic gelation method

A homogenous polymer mixture was produced by dispersing the cross-linking agent and polymer in the purified water using this approach. Copolymers could be used alone or in conjunction with this. To make sure the medication was evenly distributed in the polymer mixture, it was stirred vigorously with a magnetic stirrer after addition. The gelation medium was prepared by mixing 2% glacial acetic acid with a calcium chloride solution. The gelation media was filled with the consistent alginate solution by means of a syringe needle. After retrieval, the microsphere was washed twice with distilled water and left to dry for twenty-four hours at room temperature. [22]

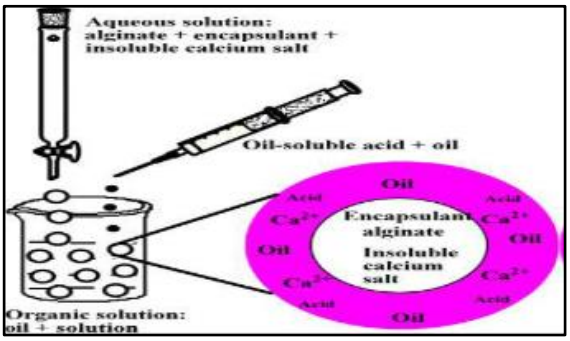

Fig. 5 Ionic gelation method

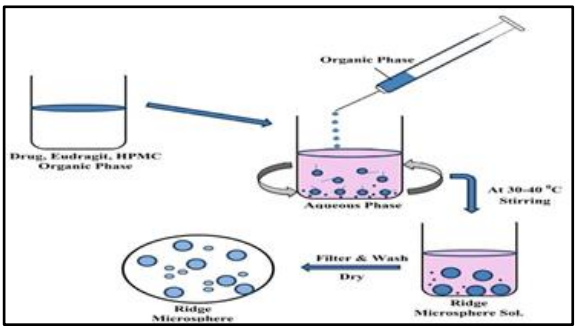

Fig. 6 Ionic gelation method

Oil-In-Water Emulsion Solvent Evaporation Technique

The polymer must be dissolved in a water-immiscible solvent for this process, and the drug must also not dissolve in water [28]. Here, organic solvents like chloroform, ethyl acetate, or dichloromethane dissolve the polymer. To make an oil-in-water emulsion, the medication is first dissolved or dispersed into a polymer solution with the help of a surfactant or emulsifying agent. Then, this drug-containing solution is emulsified into an aqueous phase. Continuous swirling or heating and pressing is used to remove the organic solvent after a stable emulsion has

developed. Because of this, microspheres develop cavities. [23]

Oil-in-Oil Emulsification Solvent Evaporation Technique

It is also known as oil-in-oil emulsification, water-in-oil emulsification, or some other term for this solvent evaporation method that is not based on water. The drug and polymers are co-dissolved in polar solvents like ethanol, dichloromethane, acetonitrile, etc., then vigorously mixed at room temperature using this approach to produce a uniform drug-polymer dispersion. Heavy and light liquid paraffin, along with an oil-soluble surfactant such as Span, make up the dispersion medium, to which this mixture is applied gradually. Two or three hours of room-temperature agitation with an overhead propeller agitator running at 500 revolutions per minute is required to ensure complete solvent evaporation (rpm). Separating the microparticles from the liquid paraffin follows decanting the mixture, followed by filtration using Whitman filter paper, three washes in n-hexane, and twenty-four hours of air drying. [24]

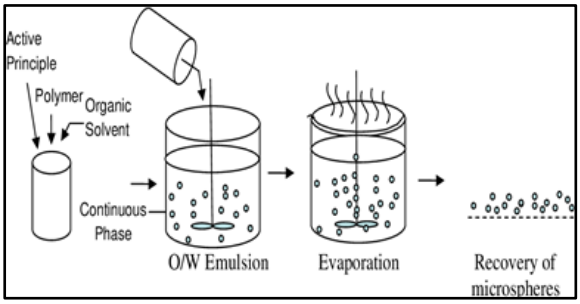

Fig 7. Oil-in-Oil Emulsification Solvent Evaporation Technique

Ionotropic Gelation Method

To make a gel matrix, this method involves cross-linking the polyelectrolyte in the presence of counterions. In the past, this method has been used to encapsulate numerous drugs. Sodium alginate is one example of a polyelectrolyte that has a particular anon that can coat the drug core and prevent its release. When these anions combine with polyvalent cations, a gelation structure called a meshwork is formed. To make microspheres, a polymeric solution with medicine is injected into a water solution with polyvalent cations using a syringe. The limerick droplets containing the medication create a three-dimensional lattice of ionically cross-linked moieties as cations diffuse into them. Schizophrenic particles. [25]

Polymers Used in Floating Microspheres

A wide range of materials, including some that are biodegradable and others that are not, have been investigated for potential use in microsphere production. Polymers, both synthetic and natural, and semisynthetic compounds are all part of this category of materials. You can make microspheres out of polymers that attract water or ones that repel it. [22]

Hydrophilic polymers

They include chitosan, gelatin, agar, egg albumin, starch, and cellulose derivatives including HPMC and DEAE cellulose.

Hydrophobic polymers

Ethyl cellulose, polylactic acid, acrylic acid esters, and polymethyl methacrylate are all part of this category.

Biodegradable polymers

Similar to how these chemicals progressively exit the administration site, hydrolysis is the chemical mechanism that causes this to happen. Some examples include polycaprolactone (PCL), polyglycolic acid (PGA), and polylactic acid (PLA), as well as other

broad classes such as polyanhydrides and poly orthocenters. [26]

Non-Biodegradable Hydrophobic Polymers

The compounds are taken or recovered from the site of administration in an undamaged state, and they do not undergo any further activity while in the environment of use. Materials such as Carcoat, Eudragit S, Ethyl cellulose, Polyethylene vinyl acetate, [27]

Hydrogels

These polymers expand when exposed to water, yet they remain insoluble. One-way hydrogels help with drug delivery and release is by creating a barrier that slows things down. Like hydrophobic polymers, they are inert and may be withdrawn intact from the site of administration. Polyacrylamide, cross-linked polyvinyl alcohol, cross-linked polyvinyl pyrrolidone, and polyhydroxy ethyl methyl acrylate are some examples. [27]

Soluble polymers

These polymers have a low molecular weight and are water-soluble without being cross-linked (less than 75,000 Daltons). The rate of solubility decreases as the molecular weight increases. Devices that degrade over time can be made using these chemicals alone or in combination with hydrophobic polymers. One example is the polyethylene glycol (PEG) copolymer, another is the hydroxyl propyl methyl cellulose (Methocel) copolymer, and still another is the uncross-linked poly vinyl alcohol or poly vinyl pyrrolidone. [28]

Factors to be Considered during Formulation

Addition of polymer solution

The polymer solidified and built up on the surface of the aqueous phase due to the high surface tension of water, as previously stated. A recently developed method was used to deliver the polymer solution into the water phase, enabling continuous microsphere formation while reducing the amount of interaction between the solution and the air-water interface. Without touching the water's surface, the polymer solution is to be delivered through a glass tube immersed in an aqueous phase, according to the technique. The microsphere yield was enhanced while the amount of aggregate formation was minimized by this approach. [29]

Effect of rotation speed

The size distribution and production of the microspheres are clearly affected by the rotation speed of the propeller. Propeller rotation speed is inversely proportional to particle size. [29]

Effect of temperature

Since the temperature of the dispersion medium regulates the pace at which the solvents the formation of microspheres, it is essential that it evaporate. Microspheres made at a low temperature (10ºC) were crushed and exhibited an irregular shape. The process makes the microsphere's shell translucent as the ethanol and dichloromethane diffuse more slowly. At 40ºC, the microsphere's shell became thinner. This could have been due to the rapid diffusion of the droplet's alcohol into the aqueous phase or the rapid evaporation of the dichloromethane upon addition to the medium. [30]

Evaluation of Floating Microsphere

Characterizing floating microspheres is a significant occurrence that helps in

assessing a suitable drug delivery technique. Floating microspheres have the following properties:

Particle size analysis

The size of floating microspheres can be measured using optical microscopy, and their size can be distributed using sieving. This is useful for calculating the average particle size with a calibrated ocular micrometre. [31]

Percentage yield

Floating microsphere percentage yields can be calculated using the following formula [46-48]: Floating microsphere weight divided by total excipient and medication weight, then multiplied by 100, is the percentage yield. In order to get this yield, the entire number of nonvolatile components needed to manufacture floating microspheres is divided by the product's actual weight. [32]

Drugentrapment efficiency

One way to determine the drug concentration in floating microspheres is to dissolve the weighted number of crushed microspheres in the required amount of 0.1 N HCl. Then, using the calibration curve, one can analyse spectrophotometrically at a given wavelength. The medication content should be verified in three different batches. One way to find out how well floating microspheres entrap drugs is to divide their actual drug content by their prospective drug content. [33]

Surface morphology

Floating microspheres' surface characteristics are investigated by scanning electron microscopy. Gold dust is vacuum-coated onto samples before they are visible. It is necessary to produce cross sections in order to observe the microspheres' interior structure and core. For the purpose of studying the internal and external morphology of floating microspheres, these studies are useful [34].

Swelling ratio

In a glass beaker set at 37 ± 0.5°C, immerse a certain mass of microspheres in 0.1 N HCl or phosphate buffer pH 6.8 for the required duration to study their swelling behavior. The microspheres are removed at different intervals after they have had a chance to inflate. [35]

In vitro drug release studies

At a temperature of 37±0.5°C, the drug release rate from hollow floating microspheres is evaluated using a USP dissolving device type I or type II. To conduct the dissolution test, 900 mL of a 0.1 N HCl dissolving fluid is spun at 100 rpm for the specified amount of time. The volume of the dissolving liquid is maintained constant by periodically removing aliquots of a predetermined volume and adding fresh aliquots of the same volume. Prior to analysis with a UV spectrophotometer, the sample solutions are filtered via Whatman filter paper. [36]

Buoyancy studies

The microspheres are dispersed over a pH 1.2 simulated stomach fluid containing the surfactant in order to perform in vitro floating tests in a USP type dissolving test device. In order to stir, the temperature must be 37±0.5°C and the speed must be 100 rpm. The ratio of floating to settling microspheres is measured at regular intervals. Next, we use formula [40] to estimate the floating microspheres' buoyancy. The mass of the settled microspheres is denoted by Qs,

while the mass of the free-floating ones is Qi. [37]

Buoyancy % = Qf / Qf + Qs * 100

Hausner's ratio

In order to determine Hausner's ratio for floating microspheres, one can use the equation to compare the tapped density with the fluff density.

Hausner's ratio = tapped density/fluffy density

In vivo studies

In vivo studies typically employ male albino rabbits that are in good health and weigh two to three kilos. The animals are given complete freedom to eat and drink throughout the trials, although they are required to fast for a whole day before to them. Every so often, two milliliters of blood are collected from the vein just outside the ear using a centrifuge that has been heparinized. In their study, Sato et al. recruited healthy human participants to participate in an in vivo experiment. To find the pharmacokinetic parameters, we analyzed data from urine excretion. [38]

Applications of Floating Microspheres

Sustained Drug Delivery

Because the medicine can stay in the stomach for lengthy durations, it can be released gradually from these systems. Thus, these strategies tackle the issue of the short stomach residence time of oral CR formulations. The systems are able to float on the contents of the stomach because their bulk density is less than 1. The pyloric aperture is too small to accommodate these systems. [39]

Site-Specific Drug Delivery

These systems work wonders for medications that are absorbed selectively from the small intestine or the stomach, such as riboflavin and furosemide. Gastritis, esophagitis, stomach and duodenal ulcers, and Helicobacter pylori can all be efficiently treated with floating microspheres' local drug release, which creates high drug concentrations at the gastric mucosa. [40]

Absorption Enhancement

When it comes to dispersing drugs that are either insoluble or only partially soluble, floating microspheres work wonders. When the solubility of a medication decreases and there is less time for drug disintegration, transit time is known to have a substantial impact on pharmaceutical absorption. At pH levels above acidic, drugs with weak bases might dissolve very slowly, making them vulnerable to empty. [41]

As carriers

Floating multiarticulate are a viable delivery mechanism for drugs with "absorption windows," including antibiotics, antiviral medicines, penicillin's, cephalosporins, aminoglycosides, and tetracyclines, among others. Certain locations on the gastrointestinal mucosa are responsible for medication absorption. The potential advantages of pharmacokinetics Multiple recent publications have demonstrated the numerous potential benefits of floating dose forms, which are sustained release approaches. It is possible to enhance the absolute bioavailability and maximize absorption of drugs that have restricted absorption in the upper gastrointestinal tract through effective administration of these drugs [42].

Conclusion

A dosage form's half-life in the stomach is proportional to the complexity and

unpredictability of the gastrointestinal tract's drug absorption process. The use of floating microspheres as gastroprotective dosage forms allows for the precise regulation of drug release to a specific region, which greatly enhances healthcare. Optimized multi-unit floating microspheres are expected to provide doctors with more bioavailable, secure, and cost-effective formulation choices for the efficient treatment of various ailments. Innovative controlled and delayed release oral formulations are within reach, thanks to these technologies, which also push the boundaries of state-of-the-art pharmaceutical discovery. In addition, there is little doubt that the present state of pharmaceutical research will offer promising prospects for the development of novel and effective approaches to the development.

Consent for Publication

All the author approved the manuscript for Publication.

Availability of data material

All required data is available.

Conflicts of interest

The authors have declared no conflicts of interest.

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Authors' contributions

All the authors have contributed equally.

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