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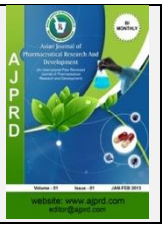

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Review Article

The Latest Advancements: A Comprehensive Review of Microballoons for Enhanced Gastroretention

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ABSTRACT

Because of their potential to remain in the gastric region for extended periods of time, gastro-retentive drug delivery methods hold great promise in oral treatment. This improves medication solubility, resulting in increased bioavailability and decreased drug waste. To achieve gastro-retentive qualities, various ways have been proposed, with microballoons in the form of hollow microspheres being a commonly investigated possibility. These microballoons, which are hollow spherical particles with no central core and have a size of less than 200 micrometers, provide an excellent method of managing medication release with site-specific absorption. Floating microballoons release via gastro-retentive mechanisms, effectively increasing bioavailability and providing a viable remedy for stomach retention. Hollow microspheres with optimized properties have the potential to revolutionize new drug delivery, particularly for secure, targeted, and efficient in vivo delivery. They represent a promising approach to gastric retention, reducing variability in plasma drug concentrations. This review provides insights into recent advances in formulation methods, evaluation techniques, the use of polymers in microballoons, and their applications as gastro-retentive drug delivery systems with controlled release capabilities.

KEYWORDS: Microballoons, Gastric retention, Preparation, Floating system,

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INTRODUCTION

Microballoons, in a strict sense, are spherical vacant particles and serve as gastro-retentive drug delivery systems following a non-effervescent approach. These microballoons are ideally less than 200 micrometres in size, categorically containing proteins or synthetic polymers. They are characterized as free-flowing powders Gastro-retentive Microballoons are low-density systems designed to possess sufficient buoyancy, allowing them to float atop gastric contents and maintain an extended presence within the stomach. This property facilitates the slow release of drugs at a desired rate, leading to increased gastric retention and a reduced need for frequent dosing. As a result, a more effective therapeutic impact can be achieved for drugs with short half-lives. Moreover, this buoyancy-induced extended gastric retention also enhances the absorption of drugs that only solubilize in the stomach.

The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in Pharmaceutics.

Gastroretentive drug delivery is an approach to extend gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects Gastroretentive dosage forms can endure in the gastric region for longer periods and, as a result, remarkably extend the gastric retention time (GRT) of drugs.

Oral administration is the most favoured and suitable means for delivering drugs into the systemic circulation. Recently, oral controlled release drug delivery has gained increasing interest in the pharmaceutical field, aiming to achieve improved therapeutic outcomes, including ease of dosing administration, patient adherence, and formulation flexibility.

The maintenance time in the gastric region has been reported to be prolonged with large single-unit dosage forms. After oral administration of this system, their size increases, inhibiting gastric emptying, even when the pyloric sphincter is in a non-contractile state due to the swelling of a balloon. Hydrogels are an example of such a delivery system.

Incorporating the drug into a floating device that is less dense than gastric fluid is a better way to enhance gastric residence time.

In recent days, extensive studies are being conducted on floating single-unit dosage forms, also known as Hydrodynamically balanced systems. However, it's important to note that these single unit dosage forms have the disadvantage of releasing their contents in an all-or-nothing manner.

If the gastric emptying process occurs before the drug starts floating, it can result in a lack of the required therapeutic activity of the drug.

On the other hand, the multi-particulate system doesn't have such issues. The uniform distribution of the multi-particulate dosage in gastric content can lead to more reproducible absorption and a reduced risk of local irritation compared to single dosage form[1].

FACTORS IMPACTING GASTRIC RETENTION

Size of the dosage form

The size of the dose form has a considerable impact on gastric retention. Dosage forms with a diameter higher than 7.5mm had a longer GRT than those with a diameter of 9.9mm.

Shape of the dosage form

The shape of the dosage form is an important factor to consider while designing a dosage form. Ring- and tetrahedron-shaped devices outperform other forms in terms of stomach retention, with GRT of 90-100% at 24 hours.

Density of a dosage form

The density of a dose form is important in gastroretention. Lower density dosage forms than gastric contents might float in gastric fluids, enabling gastroretention. High-density systems, on the other hand, tend to sink to the stomach's bottom. Both dosing regimens successfully separate the substance or treatment from the pylorus.

Nature of food intake

The type of food consumed is an important role in gastroretention. meal viscosity, meal volume, caloric content, and feeding frequency are all factors that influence dosage form retention. In general, the presence of food prolongs gastroretention. A heavy meal high in proteins and fats, for example, can improve gastroretention by 4-10 hours.

Gender, posture, and age play distinct roles in gastric retention:

Gender: Females tend to have slower stomach emptying rates than males.GRT does not differ significantly between upright, ambulatory, and supine positions. Gastric emptying slows down in the elderly[1,2].

GASTRIC PHYSIOLOGY

The stomach is structurally separated into three parts: the fundus, the body, and the antrum. The proximal fundus and body act as a repository for undigested material. The antrum is essential for mixing and works as a pump for stomach emptying via pushing action. Fasting and fed states both have gastric emptying. Fasting causes an interdigestive series of electrical impulses to cycle through the stomach and intestine every 2 to 3 hours. This cycle is broken into four phases and is known as the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC).

- Phase I (basic phase) lasts 30 to 60 minutes and is punctuated by occasional contractions.
- Phase II (before to eruption) - lasts 20 to 40 minutes with occasional action potential and contraction. As the phase progresses, so do the strength and frequency.
- Phase III (explosive phase) lasts 10 to 20 minutes. It consists of a brief period of vigorous and methodical contraction. It's known as the housekeeping wave.
- Phase IV - lasts 0-5 minutes and occurs between phases III and one of two following cycles[3,4].

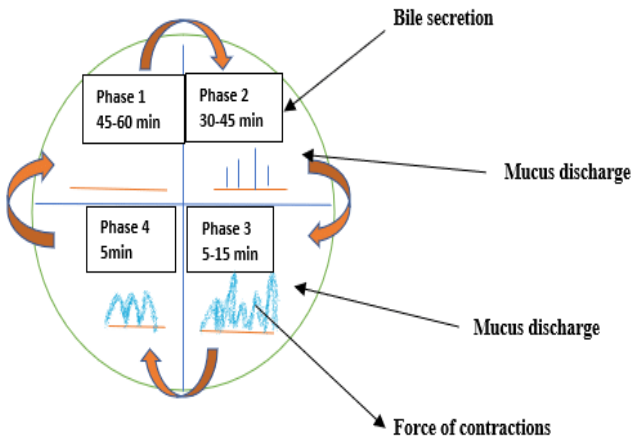


Figure 1: Phases of MMC

GASTRORETENTIVE DRUG DELIVERY SYSTEM

Floating drug delivery systems are low-density devices that have enough buoyancy to float over concentrations and increase bioavailability. These systems gradually release the medication over time, and the leftover system is evacuated from the stomach. There are two primary types of floating medication delivery devices.

Effervescent system:

a. System containing volatile liquids

b. Systems generating gas

Non-effervescent system:

a. Barrier made of colloidal gel

b. System with micro-porous compartments

c. Beads composed of alginate

d. Spheres that are hollow[4].

THE OPERATIONAL PRINCIPLE OF A BUOYANCY-BASED SYSTEM

Floating drug delivery systems (FDDS) have a lower bulk density than gastric contents, allowing them to maintain buoyancy within the stomach without affecting the gastric emptying rate over time. These systems, which are suspended atop gastric contents, gradually release the medicine at the desired rate. The leftover system is evacuated from the stomach after the medicine is administered. This results in a longer Gastric Retention Time (GRT) and better control over plasma concentration variations. A minimum stomach content and a minimum level of buoyant force are required to achieve the buoyancy retention effect[5].

Drugs:

Substances with a limited therapeutic range inside the gastrointestinal (GI) system, absorbed from the stomach and upper regions of the GI tract, exerting local effects in the stomach but degrading in the colon and disrupting normal colonic bacteria.

Aspirin, salicylic acid, ethoxybenzamide, furosemide, and other medications are examples.

Polymers:

Materials such as cellulose acetate, chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Carbopol, and Agar are examples.

Solvents:

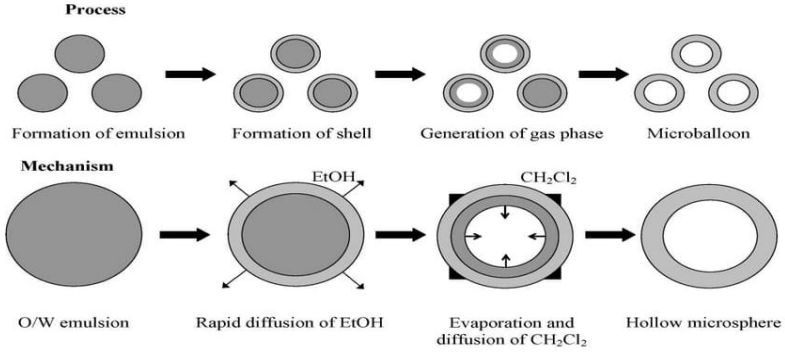
These should have good volatile characteristics and evaporate easily from the emulsion, leaving hollow microspheres behind. Ethanol, Dichloromethane (DCM), Acetonitrile, Acetone, Isopropyl alcohol, and Dimethyl formamide (DMF) are a few examples.

When the drug-polymer solution is put into it, the processing medium solidifies the drug-polymer emulsified droplets. It must not have any interaction with the former. Liquid paraffin, polyvinyl alcohol, and water are common processing media.

Surfactants:

To solidify the microspheres, stabilizers or emulsifiers are utilized. Tween 80, Span 80, and SLS are a few examples.

FORMATION PROCESS OF MICROBALLOONS



Agents of Cross-Linking:

Crosslinking chemicals can include formaldehyde, glutaraldehyde, or diacid chlorides such as Ter phthaloyl chloride.

Agents of Hardening:

Compounds used to toughen or harden microspheres. N-hexane and petroleum ether are two examples[6].

MECHANISM OF MICROBALLOONS

Microballoons are a low-density system with enough buoyancy to float above gastric fluid and remain in the stomach for an extended period of time. The medicine is given steadily and at a regulated pace while the system floats above the gastric fluid, resulting in enhanced gastric retention and fewer changes in plasma drug concentration.

When stomach fluid comes into contact with microballoons, the gel forms and the polymers hydrate, forming a colloidal gel barrier that slows fluid entry into the device.

The air retained by the inflated polymer gives the microspheres buoyancy, causing their density to be lower than that of stomach fluid. It is important to note, however, that only a small amount of gastric material is required for proper attainment of buoyancy. Assuming that the mucoadhesive characteristics of the particles have not been affected by the stomach contents, particularly non-adherent mucus, adhesion to the stomach wall during the emptying process is achievable in both fed and fasted states.

Recent developments include hollow microspheres of acrylic resins, Eudragit, Hypromellose, polyethylene oxide, cellulose acetate, polystyrene floatable shells, polycarbonate floating balloons, and Gelucire floating granules. When the gel formers, polysaccharides, and polymers of micro balloons come into touch with gastric fluid, they hydrate to form a colloidal gel barrier. This barrier regulates drug release by controlling the velocity of fluid penetration into the device.

As the external surface of the dosage form dissolves, the gel layer is maintained by the hydration of the neighbouring hydrocolloid layer. This hydration causes the air trapped in the swollen polymer to lose density and gain buoyancy[8,10].

Figure 2: Process of formation of microballoons[7].

POLYMERS USED IN MICROBALLOONS

Polymers, both natural and synthetic, are utilized in floating microballoons to deliver drugs to specific areas of the gastrointestinal tract (GIT). Polymers are macromolecule complexes made up of numerous monomer units connected by bonds.

Natural polymers such as guar gum, chitosan, xanthan gum, gellan gum, sodium alginate, and others are utilized in microballoons. Synthetic polymers such as HPMC, Eudragit, ethyl cellulose, and others are also used in microballoons[9,11].

Natural gums are high molecular weight hydrophilic carbohydrate polymers generated from plants that are insoluble in organic solvents such as ether and hydrocarbon.

Guar gum is a galactomannan polysaccharide that occurs naturally. In cold water, it hydrates and swells, generating viscous colloidal dispersions or sols. Because of this gelling ability, it is a versatile carrier for extended-release dosage formulations.

Chitosan is a natural polymer derived from chitin deacetylation. It possesses good polymer characteristics and anti-bacterial qualities, making it appropriate for site-specific delivery. Chitosan is a polycationic chemical with pKa values ranging from 6.2 to 7. When exposed to an acidic pH of 1.2 or neutral media, it becomes buoyant and offers regulated release in natural situations. The release rate of a chitosan film can be reduced by increasing its thickness.

Xanthan gum is a high molecular weight extracellular polysaccharide generated by pure culture aerobic carbohydrate fermentation. It is a polysaccharide with a long chain and a lot of trisaccharide side chains. This gum is resistant to common enzymes and has great solubility and stability in acidic, alkaline, and salt-containing conditions.

Gellan gum is a deacetylated extracellular linear polysaccharide with an anionic molecular weight. It has good flavour release, high gel strength, good consistency, works well in salt operations, and is resistant to common enzymes.

Sodium alginate is the sodium salt of alginic acid, which is a polyuronic acid combination made up of guluronic acid and d-mannuronic acid residues[10,12].

Polymers made from synthetic materials

- The pharmaceutical business makes substantial use of synthetic polymers. They serve a variety of functions, including binders and film coating agents. These polymers might be wholly synthetic or modified natural polymers, referred to as semi-synthetic.
- Hydroxypropyl methylcellulose is a water-soluble polymer that is white to off-white, odourless, and serves a variety of functions such as binding, retaining water, thickening, creating films, and lubricating. It is a semi-synthetic, inert, visco-elastic polymer that is employed as an excipient and as a controlled-delivery component in a variety of oral pharmaceuticals and commercial items. In oral capsule and tablet formulations, eudragit polymethacrylates are mostly used as film coating agents. The type of polymer utilized can result in films with variable solubility properties. Eudragit is soluble in gastric fluid at pH 5 or below, but Eudragit L, S, and FS are used as enteric coatings and are soluble at various pH levels.
- Ethyl cellulose has been widely used in the pharmaceutical business for over 50 years. It is a popular choice in pharmaceutical formulations for a variety of objectives, including taste masking of bitter substances, moisture preservation, acting as a stabilizer, and serving as an extended-release binder in inert matrix systems. It is also used to encapsulate active substances in a solvent. While the polymer's high elasticity limits its application in the wet extrusion process, it can be used as a matrix forming in conjunction with particular plasticizing agents[12,14].

TECHNIQUES USED IN THE PREPARATIONS OF MICROBALLOONS

Microballoons are prepared using many processes, with the method chosen depending on the length of drug release, route of administration, and particle size.

The various techniques of preparation are as follows:

1. Emulsion solvent evaporation technique.
2. Oil in water solvent evaporation technique.
3. Water-in-oil emulsification solvent Evaporation technique.
4. Emulsion-solvent diffusion technique.
5. Ion gelatine technique.
6. Coacervation phase separation technique.
7. Polymerization technique.
8. Spray drying and spray congealing.

Emulsion-Solvent Evaporation Technique

The medication is first dissolved in chloroform before being mixed with the polymer. The resultant solution is mixed with 0.2% sodium PVP as an emulsifier in an aqueous phase. The drug and polymer (Eudragit) are swirled at 500 rpm, leading the drug and polymer (Eudragit) to change into fine droplets that solidify into hard microballoons via solvent evaporation. After filtration, the microballoons are rinsed with demineralized water and desiccated at room temperature for 24 hours. These methods employ two fundamental systems: oil-in-water and water-in-oil[15].

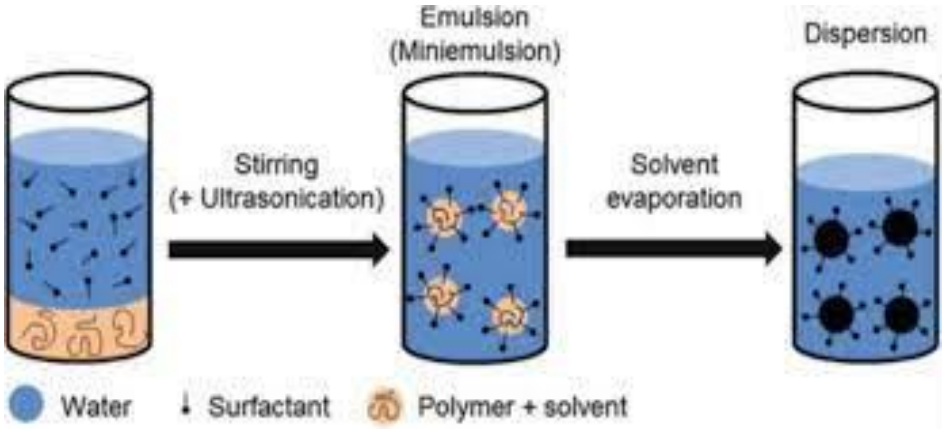


Figure 3: Emulsion-Solvent Evaporation Technique

Oil-in-Water Evaporation Techniques

Both the medication and the polymer must be insoluble in water in order for this approach to work, and the polymer must be dissolved in an immiscible solvent. The polymer is dissolved in an organic solvent, which can be dichloromethane, methanol, or chloroform. The medicine is dissolved or distributed in the polymer solution before being emulsified into an aqueous phase with an emulsifying agent to form an oil-in-water emulsion. Following that, the organic solvent is decanted, and the microparticles are separated using filtration[15,16].

Water-in-Oil Emulsification Solvent Evaporation Technique

Drug and polymer dispersion are involved in the non-aqueous emulsification solvent evaporation process, commonly known as water-in-oil emulsification. In this procedure, a mixture of light/heavy liquid paraffin and oil-soluble surfactants such as SPAN is put into the dispersion medium. The mixture is then agitated for 2-3 hours at 500 rpm using a propeller agitator to ensure complete solvent evaporation. The liquid layer is decanted after stirring, and micro-particles are separated by filtration through Whitman filter paper. They are then rinsed with n-hexane, dried for 24 hours, and ready for use[15,17].

Emulsion-Solvent Diffusion Technique

A 1:1 mixture of ethanol and dichloromethane was used to dissolve the drug-polymer mixture. This solution was added drop by drop to a sodium lauryl sulphatesolution. The resultant solution was agitated at room temperature for 1 hour with a propeller-type agitator at 150 rpm. This technique resulted in the formation of floating micro balloons. These microballoons were then cleaned and dried at room temperature in a desiccator[17,19].

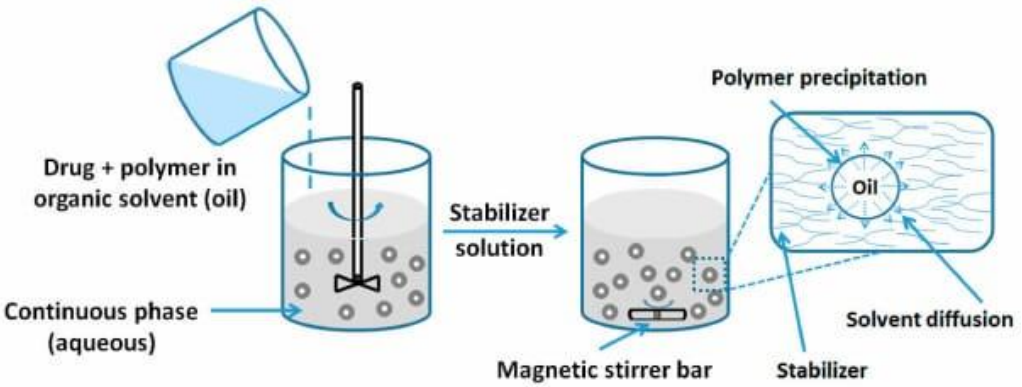


Figure 4: Emulsion Solvent Diffusion Technique.

Ionic Gelation Technique

Using the alginate/chitosan particulate approach, prepare the diclofenac sodium release system as follows: To ensure total solubility, the medication was added to a 1.2% (w/v) aqueous solution of sodium alginate and stirred continuously. The resultant solution was then added drop by drop to a solution containing Ca2+ and Al3+ ions, as well as an acetic acid-based chitosan solution. To allow internal gelation, microballoons were left in the original solution for 24 hours. Following that, the solution was filtered to separate it. It is worth noting that the highest drug release was attained in the alginate/chitosan particle system at pH 6.4-7.2[19].

Coacervation phase Separation Technique

The basis of this process is the reduction of polymer solubility in the organic phase, which results in the production of a polymer-rich phase known as co-acervation. To do this, the medication is put into a polymer solution, causing the polymer's initial phase separation, which subsequently engulfs the drug particles[19,20].

Polymerization technique

The most common polymerization processes are classified.

a. Natural polymerization: Polymerization can be accomplished using a variety of methods, including bulk, suspension, precipitation, emulsion, and micellar processes. This is referred to as natural polymerization.

b. Interfacial polymerization: This technique involves the reaction of monomers at the interface of two immiscible liquid phases, resulting in the development of a polymer film that encases the scattered components[19].

Spray drying and Spray congealing

To create the polymer, a suitably volatile organic solvent, such as dichloromethane, acetone, or methanol, is utilized. Under high-speed homogenization, the medication in solid form is disseminated in the polymer solution. The mixture is then atomized in a jet of hot air. This atomization produces microscopic droplets or mist from which the solvent evaporates instantly, resulting in the creation of microballoons of different sizes. These procedures are known as spray drying and spray congealing, depending on whether they are used to remove solvent or cool the solution[20,21].

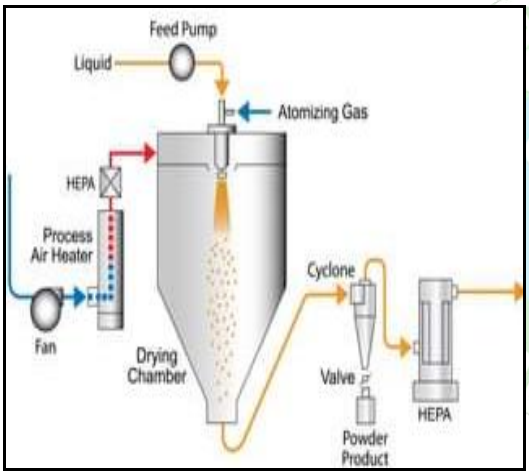


Figure 5: Spray drying and Spray congealing

FACTORS TO CONSIDERED DURING FORMULATION

Polymer Solution Addition

Water's high surface tension caused polymer solidification and build-up on the aqueous phase's surface. A unique method was developed to maintain contact between the polymer solution and the air-water interface and to produce a continuous process for microballoon preparation. This method introduced the polymer solution through a glass tube immersed in an aqueous phase, ensuring that it did not come into direct contactwith the water's surface. As a result, our method enhanced microballoon yield while decreasing aggregate formation.

The Influence of Rotation Speed

The rotation speed of the propeller clearly influences yield and size distribution of microballoons. The average particle size decreases as the propeller's rotation speed increases.

The Floating Effect Miniature balloons

The evaporation rate of these solvents is greatly regulated by the temperature of the dispensing medium, which is an important aspect in the formulation of microballoons. Microballoons made at low temperatures have uneven forms and were easily crushed. The microballoon shells become translucent during the process due to the decreased diffusion rate of ethanol and dichloromethane. The microballoon shells grew thinner at higher temperatures, probably due to the quick diffusion of alcohol into the aqueous phase and the immediate evaporation of dichloromethane upon introduction into the medium[21].

ADVANTAGES

- Reduces the severity of unwanted effects while increasing bioavailability.
- Prevents oscillations in plasma drug concentration, allowing a desired level to be maintained through continuous drug release.
- Improves stomach retention by reducing material density and buoyancy.
- Improved absorption of medicines that dissolve exclusively in the stomach.
- Achieving targeted drug delivery.
- Drug release that is prolonged and controlled.
- Improves patient compliance by lowering dosage frequency.
- Effective delivery for medications with low bioavailability due to limited upper GIT absorption, which benefits pharmaceuticals with short half-lives in particular.
- Floating Microballoons effectively enhance absorption and improve bioavailability of a variety of medicines, including furosemide and riboflavin.
- Floatation Microballoons can transport medications with absorption windows, such as antivirals, antifungals, and antibiotics. These medicines are absorbed selectively from certain sections of the GI mucosa.
- Floating microballoons containing indomethacin, for example, are extremely successful at reducing the primary side effect of stomach discomfort in nonsteroidal anti-inflammatory treatments.
- Microballoons improve pharmacotherapy considerably.
- Enhances patient compliance by lowering dosage frequency.
- Increased drug use can increase bioavailability while decreasing the frequency and severity of side effects.

Despite the first-pass impact, continual drug release ensures that plasma drug concentrations remain stable.

- A hollow microsphere is utilized to reduce material density and increase stomach retention duration. Because of buoyancy, the value increased.
- Improved absorption of drugs that dissolve exclusively in the stomach.
- Controlled drug release over a long period of time.
- Microspheres outperform single-unit floating dose types in terms of release. medication consistently and without the potential of dose variationdumping.
- Gastric discomfort can be avoided, and the therapeutic impact of short half-life drugs can be improved[20,22].

DISADVANTAGES

- Drugs that irritate the stomach mucosa are unsuitable candidates for Floating Drug Delivery Systems (FDDS).
- Nifedipine and other drugs that are absorbed throughout the whole gastrointestinal tract (GIT) and undergo first-pass metabolism may not be suitable for FDDS.
- Drugs with stomach stability or solubility concerns are unsuitable candidates for Floating Drug Delivery Systems (FDDS).
- NSAIDs, certain antibiotics, digoxin, theophylline, corticosteroids, iron (ferrous sulphate), oral contraceptives, and tricyclic antidepressants are not recommended for FDDS.
- Drugs like nifedipine, which undergo first-pass metabolism and are absorbed throughout the entire gastrointestinal tract, may not be desired.
- Unsuitable candidates for medications with stomach stability or solubility concerns include those such as ranolazine
- The "all or nothing" mentality associated with single-unit floating capsules or tablets can be solved by developing multi-unit systems such as floating microballoons or microballoons.
- Floating Drug Delivery Systems (FDDS) require a sufficient amount of fluid in the stomach to float, hence a suitable amount of water (200-250 ml) should be eaten with FDDS[20,23].

APPLICATIONS OF MICROBALLOONS

- Because of their various densities, solid and hollow microspheres serve different purposes. Hollow microspheres are often employed as additives to lower material density, but solid microspheres, depending on their composition and size, have a wide range of applications.
- Hollow microspheres help to improve stomach pharmacotherapy by allowing for localized medication release. This leads in a high medication concentration at the gastric mucosa, which is helpful for eradicating Helicobacter pylori from submucosal tissue in the stomach. This method is useful in the treatment of stomach and duodenal ulcers, gastritis, and esophagitis.
- Microsphere systems have long-term drug release characteristics, allowing for longer drug release times. Transilast hollow microspheres, for example, are used to create controlled floating medicine delivery devices.
- Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride, and Riboflavin have all recently been successfully entrapped within hollow microspheres.
- Floating Microballoons excel at delivering medications that are sparsely soluble or insoluble.Drug solubility influences drug dissolution time, with decreasing solubility limiting available time for dissolution, making transit time an important component in medication absorption. Because hollow microspheres prevent solubility from being the rate-limiting stage in the release of poorly soluble basic medicines at an alkaline pH, these medications are confined to the stomach. Drugs that are easily absorbed, such as Verapamil hydrochloride, benefit from gastric release, which increases their bioavailability.
- Deacidified polymer granules with internal cavities were applied to both acidic and neutral environments, resulting in buoyant and controlled release of the medication Prednisolone. Melatonin-containing floating microballoons demonstrated a gastro-retentive controlled-release delivery technique. In simulated stomach fluid, medication release from these microcapsules is greatly delayed, lasting 1.75-6.7 hours. Metoclopramide and other mucoadhesive microcapsules can stay in the stomach for up to 10 hours.
- •Floating Microballoons can be used as medication carriers with absorption windows. Certain chemicals, such as antiviral and antibiotic medicines, are absorbed preferentially from certain regions of the GI mucosa.
- •Nonsteroidal anti-inflammatory drug-containing hollow microspheres are particularly effective for controlled release, decreasing the principal side effect of stomach discomfort. Floating microballoons with Indomethacin, for example, provide significant benefits to rheumatic patients.
- By removing Helicobacter pylori from the stomach's submucosal tissue, floating microspheres greatly improve stomach pharmacotherapy, assisting in the treatment of illnesses such as peptic ulcer, gastritis, and gastroesophageal reflux disease. Floating bio-adhesive microspheres with acetohydroxamic acid are

designed to treat Helicobacter pylori infection. Hollow ranitidine HCL microspheres are also being developed for the treatment of stomach ulcers. Microballoons can be used as additives to lower a material's density.

- This method improves pharmacotherapy for stomach problems by enhancing local medication release. It results in a significant concentration of the antibiotic at the gastric mucosa, successfully eliminating Helicobacter pylori from the stomach's submucosal tissue. This approach is effective in treating stomach and duodenal ulcers, gastritis, and esophagitis.
- These microballoons demonstrate sustained drug release behavior, ensuring long-term drug release.
- Floating microspheres are effective at delivering both sparingly soluble and insoluble medications.
- Drugs with absorption windows, such as antiviral, antifungal, and antibiotic medicines, can be carried by floating microspheres.
- Hollow microspheres containing nonsteroidal anti-inflammatory medications are particularly effective for controlled release, lowering the risk of stomach discomfort, which is a significant side effect[21,23].

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