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REVIEW ARTICLE
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A REVIEW ON THE EMERGING POTENTIAL OF FLOATING MICROSPHERES IN GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Kuldipsinh Chauhan[1], Dr.Shweta Paroha[2*], Dr.Pragnesh Patani[3]

[1,2*,3]Khyati College of Pharmacy, Palodia, Ahemdabad

***Corresponding Author:** Dr.Shweta Paroha
*Khyati College of Pharmacy, Palodia, Ahemdabad, Email: shwetatechno86@gmail.com

Abstract
Oral drug delivery systems have to overcome a number of challenges in order to maintain drug release and extend the amount of time the medication is in the gastrointestinal tract until it has been fully consumed. A specific period of time later, fully released This procedure, called gastric emptying, It is emptied. Athletes who are having digestive problems can find it very beneficial. The upper small intestine provides a window for the absorption of nutrients. Drugs that are poorly soluble or unstable in intestinal fluids might benefit greatly from floating microspheres that improve drug retention and enable prolonged action in the stomach.
Floating drug delivery systems (FDDS) float in the stomach for a long time because of their lower bulk density than gastric fluids. Due to the possibility that floating microspheres in the stomach may lengthen a medication's retention time, the effects of the drug may remain longer. As a result, a longer drug retention time and a slower metabolism are required to assure long-term efficacy. FDDS dose forms are effective in situations of constipation and hyperactive bowel movement to elicit a significantly better reaction. Floating drug delivery systems (FDDSs) are helpful in these circumstances. They are anticipated to float on the stomach's contents for a considerable amount of time. Gastro retentive dosage forms are available in a variety of formats, such as tablets and capsules. Hollow microspheres are garnering a lot of interest due to their numerous potential uses in medicine delivery. Due to the drug substance being uniformly dispersed throughout the stomach juice, this prevents the drug from being released too soon. This review's objective is to examine floating microspheres approach in Gastro-retentive Drug Delivery System.

Keywords: Floating drug delivery systems (FDDSs), Floating microspheres, Gastro retentive dosage forms, Gastroretentive Drug Delivery System.

1. INTRODUCTION

1.1 Gastro Retentive Drug Delivery System (GRDDS):

Frequent dosing is required for those drugs which are having short half-lives, easily absorbed from the GI tract and rapidly eliminated from the systemic circulation. The GRDDS is the solution to this problem, which offers effectual drug concentration in plasma for sufficient period of time, diminishing the frequency of dosage during formulation. The GRDDS also reduce the plasma drug concentration fluctuation by drug delivery in controlled manner [1]. Different methodologies have been employed to enhance the retention of oral dosage forms in the stomach. Some dosage forms are

formulated as single component while others formulated as multi component. The GRDDS are mainly classified into floating and non-floating systems.

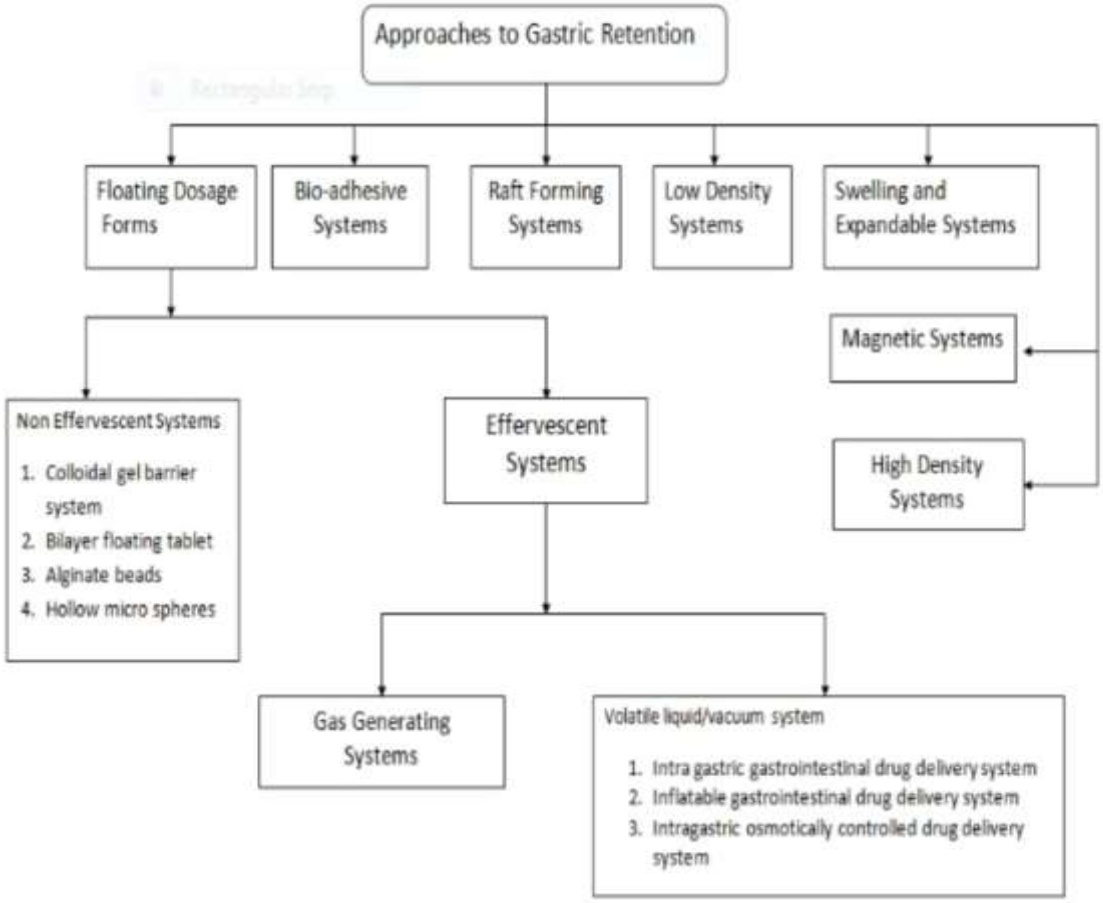

Figure 1: Different approaches for gastric retention

1.2 Floating Drug Delivery Systems (FDDS)

These have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [3,4]. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[5,6]

RW or F = F buoyancy – F gravity = (Df - Ds) Gv

Where, RW = total vertical force, Df = fluid density, Ds= object density, V = volume and g = acceleration due to gravity

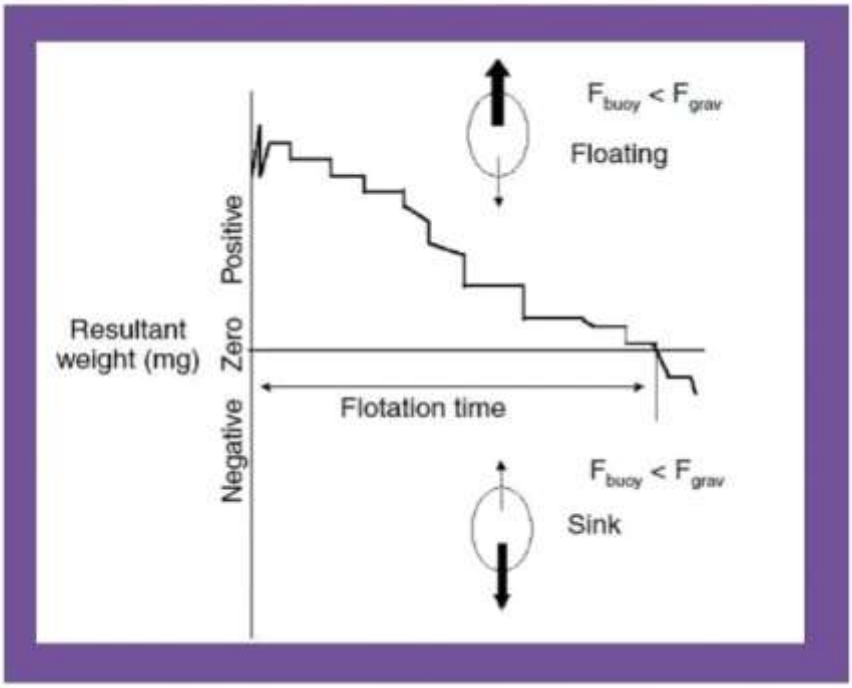

Figure 2: Effect of resultant weight during buoyancy on the floating tendency of FDDS

2. Classification of floating drug delivery system: There are mainly two systems which are classified below:

2.1 Effervescent systems

- Volatile liquid containing systems
- Gas generating systems

2.2 Non effervescent systems

- Alginate beads
- Microporus compartment systems
- Colloidal gel barrier systems
- Floating microspheres

2.3 Benefits of Floating Microspheres:

- It enhances the bioavailability.
- Able to deliver drug in sustained manner and diminished frequency of dosage
- It minimizes the drug concentration fluctuation and enhanced the selectivity for receptor activation.
- It decease the side effect in the colon and enhances the site
- Diminishes the body counter activity leads to superior drug efficiency
- Offer flexibility in designing of dosage form

2.4 Demerits of Floating Microspheres :

- To float and work effectively, FMs need high amount of fluid in the stomach.
- It is not suitable for drugs which have stability and solubility problem at GIT.
- FMs are not suitable for drugs which have stability problem in the acidic environment of stomach.

3. Polymers Employed for Floating Microspheres :

Various biodegradable and nonbiodegradable polymers have been examined for Floating Microspheres formulation.[7] These polymers are from natural, synthetic and semi synthetic origin. Floating Microspheres can be formulated by using lipophilic and lipophobic polymers.

Biodegradable polymers: These polymers include poly glycolic acid, polycaprolactone, polylactic acid, polyanhydrides and polyorthoesters

Non-biodegradable polymers: It include cellulose acetate, Acrycoat, Eudragit S, polyether urethane [8].
Lipophilic polymers: These polymers include acrylic acid esters, polymethyl methacrylate, polylactic acid, ethyl cellulose.
Lipophobic polymers: It includes derivatives of cellulose such as CMC, HPMC and chitosan, gelatin, agar, egg albumin.
Soluble polymers: These polymers include polyethylene glycol, hydroxy propyl methyl cellulose.
Hydrogels: These polymers do not dissolve after coming into contact with fluid but swell instantaneously include polyacryl amide, polyhydroxy ethyl methyl acrylate, poly vinyl pyrrolidone [9].

4. POLYMERS USED IN HOLLOW MICROSPHERES

The production of microspheres has been studied using a variety of materials, both biodegradable and nonbiodegradable; these materials include semisynthetic and natural polymers. Polymers that are hydrophilic or hydrophobic can be used to create microspheres. Hydrophilic polymers These consist of cellulose derivatives, such as HPMC and DEAE cellulose, gelatin, agar, egg albumin, starch, and chitosan [10, 11]. Hydrophobic polymers These include acrylic acid esters, PMMA, polylactic acid, ethyl cellulose, and others. Biodegradable adhesives These substances likewise gradually leave the administration site, however this happens in reaction to a chemical reaction like hydrolysis. Examples include polycaprolactone (PCL), polylactic acid (PLA), poly glycollic acid (PGA), and a number of general classes, including polyanhydrides and polyorthoesters. Hydrophobic Non-Biodegradable Polymers [12,13].

These substances are removed or retrieved undamaged from the administration site, and they are inactive in the environment of usage. Examples include polyethylene (PE), polyvinyl chloride (PVC), ethylene cellulose (EC), polyethylene vinyl acetate (EVA), polyether urethane (PEU), Acrycoat, Eudragit S, and others. Hydrogels When these polymers come into contact with water, they swell but do not disintegrate. Similar to hydrophobic polymers, hydrogels are inert, can be removed whole from the administration site, and work by creating a barrier that limits the pace at which medications can be transported and released. For instance, polyacryl amide, cross-linked polyvinyl alcohol (PVA), cross-linked polyvinylpyrrolidone (PVP), and polyhydroxy ethyl methyl acrylate (PHEMA). Soluble polymers are uncross-linked polymers with a moderate molecular weight (less than 75,000 Daltons) that dissolve in water [14,15]. As molecular weight increases, the rate of dissolution lowers. These substances can be combined with hydrophobic polymers or used alone to create devices that gradually degrade. Examples include copolymers of methacrylic acid, hydroxyl propyl methyl cellulose (Methocel), uncross linked polyvinyl alcohol or polyvinyl pyrrolidone, and polyethylene glycol (PEG)[16, 17] .

POLYMER	ACTION
Modified starch, HPMC, Carbopol 974P	Slower release of drug
Ethyl Cellulose	Controlled release for longer period of time.
PLGA, Chitosan	Vaccine delivery.
PLA, PLGA, Starchcyanoacrylateetc(PEG-) liposomes	Drug delivery without toxic side effects
Magnetic polystyrene microspheres	Specific cell labelling
Polymer resins such as Agarosepolyacroline, sephadex	Affinity chromatography
Chitosan coated PlGA microspheres	Targeted drug delivery
Polyvinyl alcohol, polyacrylamide	Adsorption of harmful substances in blood

Figure 3: Polymers used in microspheres[18]

5. POTENTIAL DRUG CANDIDATES FOR GRDDS

The short window in the gastrointestinal tract when levodopa and riboflavin are found .Chlordiazepoxide, cinnarizine, and calcium supplements are examples of substances that are mostly absorbed from the stomach and upper portion of the gastrointestinal tract.Medication that acts locally in the stomach, like misoprostol and antacids; medication that breaks down in the colon, like metronidazole and ranitidine HCl [19,20,21] . Medication that disrupts common colonic bacteria, such as amoxicillin trihydrate DF comes in two forms: low-density, which gives gastric fluid buoyancy, and high-density, which stays intact in the stomach's bottom.Slow GIT motility caused by concurrent medication or excipient delivery; Bioadhesion to abdominal mucosa. A larger-scale inflammation or spread that prevents DF from passing through the pyloric sphincter.

6. Classification of Floating Drug Delivery Systems

Floating drug delivery systems can be classified into two types [22]

- Effervescent systems
- Volatile liquid containing systems
- Gas-generating Systems
- Non-Effervescent Systems
- Colloidal gel barrier systems
- Microporous Compartment System
- Alginate beads
- Hollow microspheres

6.1 Effervescent Floating Dosage Forms : This approach provides floating drug delivery systems based on the formation of CO2 gas. It utilizes effervescent components such as sodium bicarbonate (NaHCO3) or sodium carbonate, and additionally citric or tartaric acid. Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme. Generally effervescent systems suffer from the disadvantage not to float immediately after swallowing because the process of gas generation takes some time. Therefore, they could be cleared from the stomach before becoming effective. The performance of low-density, floating drug delivery systems is strongly dependent on the filling state of the stomach [23].

6.2 Non-Effervescent Floating Dosage Forms : This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the ‘plug type systems’ since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms [24].

6.3 Colloidal gel barrier system : These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxy methyl cellulose (NaCMC), poly carbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydro dynamically balanced system capsules. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form [25,26].

6.4 Microporous compartment system : This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to prevent any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid. Gastric fluid enters through the aperture, dissolves the drug and dissolved drug moves for continuous transport across the intestine for drug absorption [27].

6.5 Alginate beads : Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, leading to the formation of porous system, which can maintain a floating force over 12 h [28,29] .

6.6 Hollow microspheres or floating microsphere : Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres (microballoons) are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200µm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration [30] . Hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion or solvent evaporation methods to prolong the gastric retention time (GRT) of the dosage form with continuously floating over the surface of an acidic dissolution media containing surfactant for more than 12 h [31, 32] .

7. MECHANISM OF FLOTATION OF MICROSPHERES

The gel formers, polysaccharides, and polymers in microspheres hydrate when they come into contact with stomach fluid, creating a colloidal gel barrier that regulates the rate at which fluid enters the device and, in turn, the release of drugs. The gel layer is kept intact by hydrating the nearby hydrocolloid layer as the dosage form's outer surface dissolves. The inflated polymer traps air, which reduces density and gives the microspheres buoyancy. However, in order to properly achieve buoyancy, a minimal amount of stomach content is required [33,34].

8. METHOD OF PREPARATION OF FLOATING MICROSPHERES

Gastro retentive floating microspheres can be created using a variety of developing procedures. Nonetheless, many scientists throughout the world have used the solvent evaporation and ionotropic gelation techniques extensively to investigate the various aspects of floating microspheres. Selecting the best technique is crucial for the effective trapping of active ingredients when creating floating controlled release microspheres. The type of medication, the polymer, and the intended purpose all influence the fabrication procedure choice [35] .

The characteristics of the materials and the process engineering elements have a significant impact on the microspheres' properties and the controlled release rate that results.

8.1 Solvent evaporation technique

The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additive (surfactants or polymer) to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the oil-water interface of droplets, forming cavity and thus making them hollow to impart the floating

properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide and polycarbonate [36, 37] .

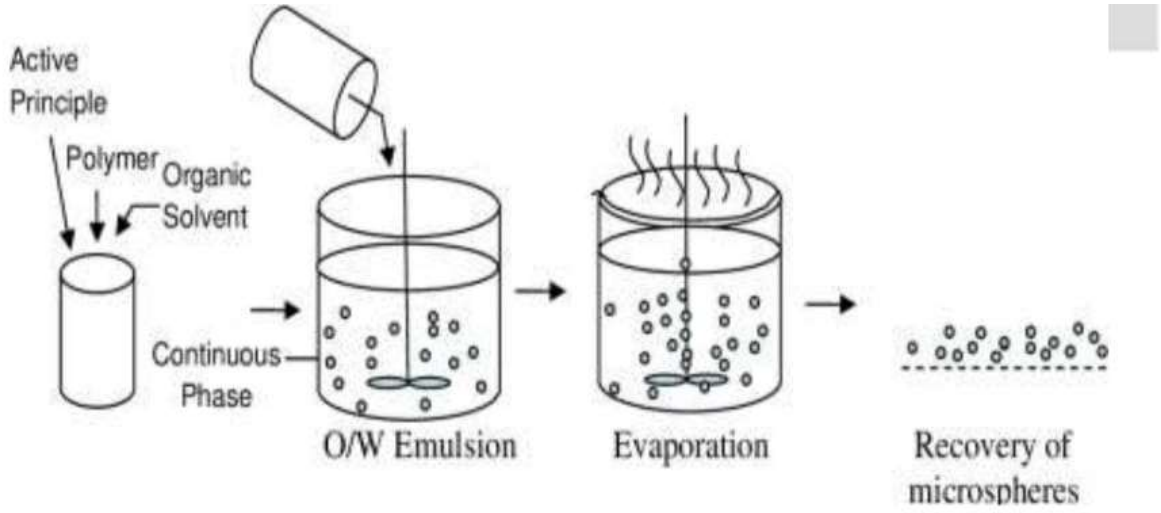

Figure 4: Solvent evaporation technique

8.2 Oil in water emulsion solvent evaporation technique

The medication and the polymer used in this procedure should both be insoluble in water, and the polymer needs a solvent that is water immiscible. This approach involves dissolving the polymer in an organic solvent, either alone or in combination, such as dichloromethane, chloroform, or ethyl acetate. A surfactant or emulsifying agent is used to dissolve or distribute the medicine into a polymer solution, which is then emulsified into an aqueous phase to create an oil-in-water emulsion. Once a stable emulsion has formed, the organic solvent is removed by swirling continuously or by raising the temperature under pressure. The size and shape of the embryonic microspheres are determined by the elimination of the solvent [38] . Polymer precipitation at the o/w interface has been seen as a result of the embryonic microspheres' quick solvent clearance. This causes a cavity to form in the microspheres, giving them a hollow structure that allows them to float.Because it is easier to make and requires less cleanup after use, oil-in-water emulsion is more commonly utilised than water-in-oil [39] .

8.3 Oil-in-Oil Emulsification Solvent Evaporation Technique

This oil-in-oil (sometimes referred as water-in-oil) emulsification process is also known as non-aqueous emulsification solvent evaporation. In this technique, drug and polymers are codissolved at room temperature into polar solvents such as ethanol, dichloromethane, acetonitrile etc. with vigorous agitation to form uniform drug–polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at 500 revolutions per minute (rpm) and room temperature over a period of 2–3 h to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the microparticles are separated by filtration through a Whitman filter paper, washed thrice with n-hexane, air dried for 24 h and subsequently stored in desiccators. Span 60 is generally used which is non-ionic surfactant. Span 60 has an HLB value of 4.3 and acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium [40] .

8.4 Ionotropic Gelation Method

This process creates a gel matrix by cross-linking the polyelectrolyte in the presence of counter ions. This method has typically been used to encapsulate a large number of medications. Certain anions

are present in the chemical structure of polyelectrolytes, like sodium alginate, which have the ability to coat the drug core and function as a release rate retardant. These anions combine with polyvalent cations and induce gelation to form a meshwork structure. Using a syringe, drop drug-loaded polymeric solution into the aqueous solution of polyvalent cations to create microspheres. The cations produce a three-dimensional lattice of ionically cross-linked moieties when they diffuse into the drug-loaded lymeric droplets. After being created and allowed to remain in the original solution long enough for internal gelification, the microspheres are filtered out. In the creation of floating microspheres, natural polymers like alginates are frequently utilised to enhance drug trapping [41,42] .

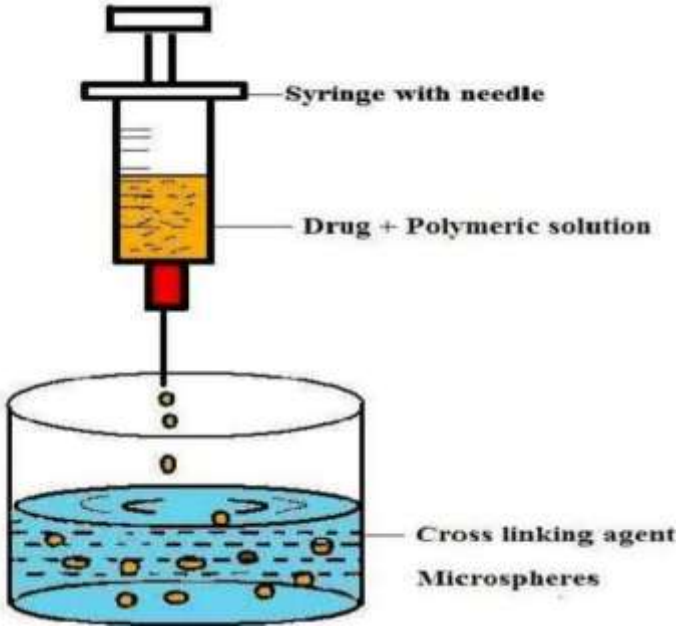

Figure 5: Ionotropic gelation method

8.5 Emulsion Solvent Diffusion Method

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible (Figure 5). The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse in to the droplets by which drug crystallizes. (43, 44, 45)

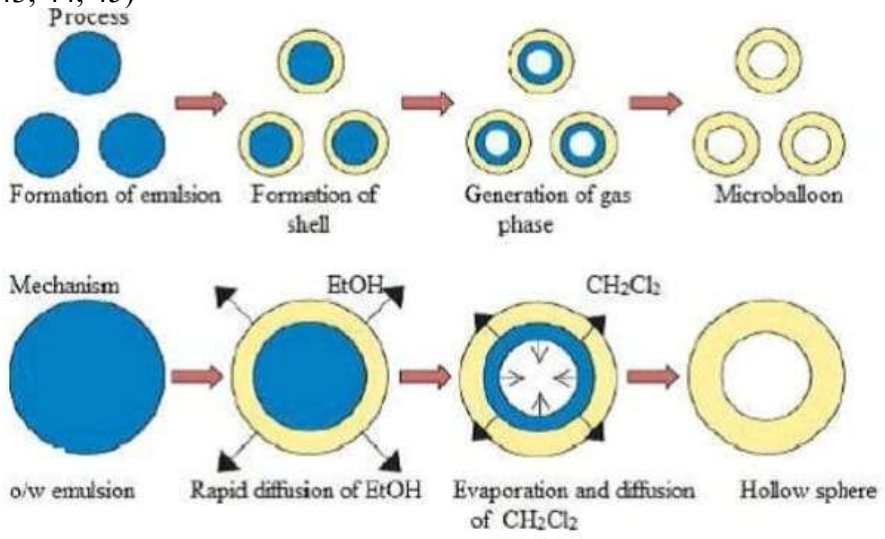

Figure 6: Preparation technique (emulsion-solvent diffusion method) and mechanism of 'microballoon' formation

9. EVALUATION OF FLOATING MICROSPHERES

Micromeritics:

Microspheres were characterized for their micromeritics properties such as particle size, angle of repose, compressibility index and Hausners ratio.

Particle size :

The particle size of the microspheres was measured using an optical microscopic method and mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

Bulk density:

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10 gm sample of granules was placed into 25 ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and the bulk density was calculated using the equation (values expressed in gm/cm3)

Bulk density = weight of sample/volume of sample

Tapped density :

Accurately weighed 10 gm of powder sample was placed in 25 ml measuring cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume was recorded and the tapped density was calculated by the following equation (values expressed in gm/cm3)

Tapped density = weight of sample/Tapped volume

Carr's index (%) :

The Carr's index is frequently used as an indication of the flowability of a powder. A Carr's index greater than 25% is considered to be an indication of poor flowability and below 15% of good flowability. Flow property of blend depends upon Compressibility index. The Carr's index is an indication of the compressibility of a powder. It is calculated by the formula. (Values as given in Table 1)

Carr's index (%) = Tapped density – Bulk density/Tapped density x 100

Carr's index	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Table 1: Carr's Index as an Indication of Powder Flow

Angle of repose (θ):

The angle of repose is indicative of flowability of the substance. Funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters. The angle of repose is calculated by (Values as given in Table 2).

Tan θ = h/r

Therefore, θ = tan-1 h/r

Angle of Repose(θ)	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

Table 2: Relationship between ange of repose (θ) and flowability.

Hausner's ratio :
The Hausner's ratio is an indication of the compressibility of a powder. It is calculated by the formula,

Hausner's ratio = Tapped density/Bulk density x 100
The Hausner's ratio is frequently used as an indication of the flowability of a powder. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. The observations for the flow properties determinations were recorded.

Drug entrapment efficiency (DEE):
The microspheres were crushed and repeatedly extracted using aliquots of 0.1N HCl to quantify the amount of drug contained. After transferring the extract to a 100 ml volumetric flask, 0.1N HCl was added to adjust the volume. A spectrophotometer was used to test the absorbance of the filtered solution against a suitable blank. Using the following calculation, the amount of medication trapped in the microspheres was determined.
DEE = (amount of drug actually present/theoretical drug load expected) × 100

Swelling studies:
The molecular properties of swelled polymers were calculated by swelling studies. A variety of advanced techniques, such as H1 NMR imaging, confocal laser scanning microscopy (CLSM), cryogenic scanning electron microscopy (Cryo-SEM), light scattering imaging (LSI), and dissolving apparatus, can be used to determine swelling investigations.Using a dissolution equipment, the swelling studies were computed using the following formula.

Swelling Ratio = Weight of wet formulations /Weight
Scanning Electron Microscopy (SEM):
The SEM method was used to determine the surface morphology. Using double-sided sticky tape, the microcapsules were placed directly on the SEM sample slab in this instance, and under low pressure, they were covered in gold film.

In-vitro buoyancy:
A USP XXIV dissolution apparatus type II holding 900 ml of 0.1 N hydrochloric acid with 0.02% tween 80 was covered with 300 mg microspheres. A paddle that rotated at 100 rpm for 12 hours was used to stir the medium. The microspheres' settled and floating parts were collected independently. After drying, the microspheres were weighed. The ratio of the mass of the microspheres that stayed afloat to the overall mass of the microspheres was used to compute the buoyancy percentage.
Buoyancy (%) = Wf/ Wf+Ws x 100
Where, Wf and Ws are the weights of the microspheres that are floating and settled, respectively.

In-vitro drug release studies:
The USP dissolving device at a specific speed is utilised for these kinds of investigations. The temperature of the distilled water and dissolving fluid is kept at 37±10C. Samples are taken out

periodically and subjected to spectrophotometric analysis. To keep the washbasin condition stable, the capacity was refilled with the same quantity of freshmedium [46] .

10. Applications of Floating Microspheres

Sustained Drug Delivery:

These systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g. riboflavin and furosemide. Floating microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating Helicobacter pylori from the submucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis [47] .

Absorption Enhancement:

Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability [48,49] .

As Carriers:

The floating multiparticulates can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa. Pharmacokinetic advantages and future potential: As sustained release systems, floating dosage forms offer various potential advantages evident from several recent publications. Drugs that have poor bioavailability because their absorption is restricted to the upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bio availabilities [50] .

11. Recent Advancement of Gastro Retentive Floating Microspheres:

Nila et al developed sustained release gastro retentive FMs of carvedilol (CVD) with the help of emulsion solvent diffusion approach to enhance its residence time inside the stomach. The formulation was optimized by employing 32 full factorial designs. The researchers revealed that particle size, entrapment efficiency of drug and in vitro release of drug were dependent on speed of stirring and ethyl cellulose concentration. The fabricated microspheres exhibited the buoyancy for more than 10 h and exhibited sustained action of drug. The investigators concluded that FM-CVD have excellent buoyancy along with noteworthy sustained release of CVD [51,52] . Abbas et al developed FMs of enalapril (ENA) to increase its bioavailability and absorption with the help of ionotropic gelation method employing a carrier of hydrophilic nature. The researchers exhibited that optimized formulation gives maximum drug release around 92%. The FMs-ENA exhibited excellent entrapment efficiency of drug, good buoyancy and significant % yield. The investigators concluded that fabricated FMs have the potential to deliver the drug in controlled manner and also enhance the

patient compliance [53]. Gupta et al formulated and evaluated silymarin (SLM) FMs to enhance the bioavilability of drug and increase the gastric residence time. The researchers revealed that fabricated FMs-SLM enhanced the release of drug for 12 h and were buoyant for same period of time. The drug release mechanism followed non-fickian pattern and kinetics of release of drug was Higuchi. The investigators concluded that FMs-SLM showed significant release of drug in gastric environment for 12 h and also enhance the drug bioavailability along with patient compliance. 20 Palanivelu et al prepared and evaluated Ranitidine (RTD) FMs with the help of ionotropic gelation and solvent evaporation approach employing various polymers such as chitosan, Carbopol and sodium alginate. The researchers showed that FMs particle size was enhanced as enhancing the polymer concentration. The optimized formation exhibited noteworthy entrapment efficiency of drug around 88%. The in vitro buoyancy range of FMs was in between 67% to 82%. The in vitro drug release for optimized formulation was around 94%. The researchers concluded that FMs-RTD have the potential to release the drug long period of time in the stomach, also will enhance the bioavailability and patient compliance. 21 Rathod et al fabricated FMs of Felodipine (FLD) equipped with fibroin and sodium alginate exhibited modified drug release. The researchers employed spray drying method to formulated FMs using binary polymer system of sodium alginate and fibroin. The investigators exhibited that floating lag time for optimized formulation was in the range of 10 to 15 sec and floating time was more than 12 h. The in vitro drug release for optimized formulation was 81.34% to 85.98% and floating buoyancy was 97.56±0.87%. The FMs of FLD was successfully fabricated due to significant electrostatic repulsion between the polymers. As per USFDA guidelines, the fabricated FMs exhibited noteworthy floating behavior and extended drug release for > 12h. The researchers concluded that sodium alginate and fibroin could be employed in future to fabricate different floating systems having dissimilar solubility profiles [54,55,56] .

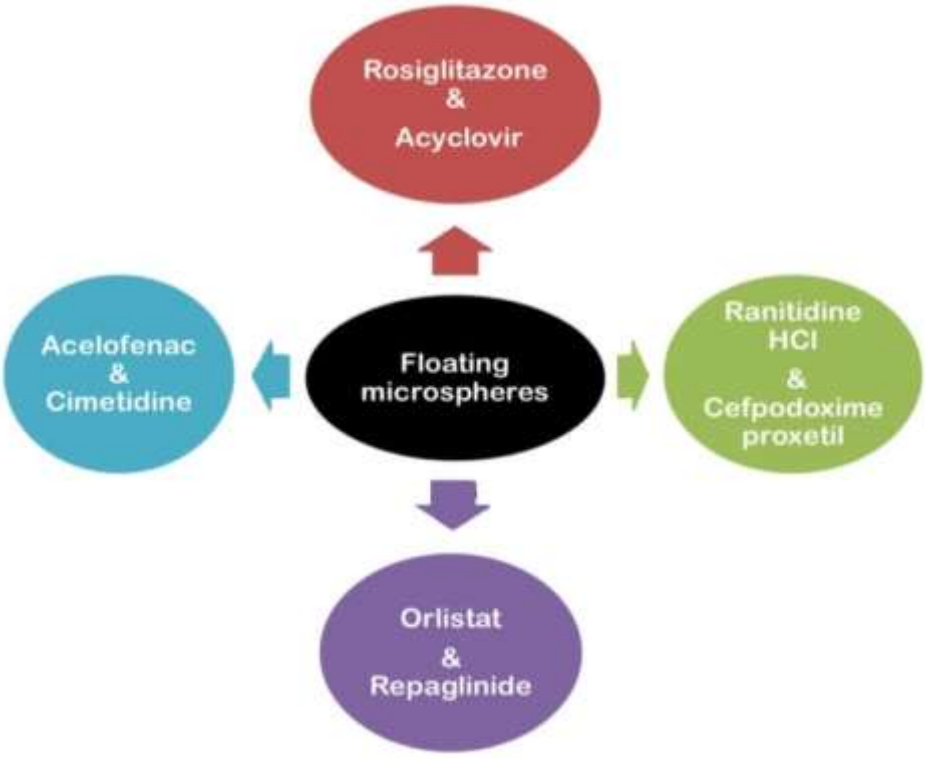

Figure 7: Drugs formulated as floating microspheres

12. CONCLUSION

Drug absorption in the gastrointestinal tract is a very unpredictable process, and the duration of drug absorption is increased by maintaining the dosage form in the stomach. With their ability to precisely control the release rate of a target medicine to a specific region, floating microspheres as gastroretentive dosage forms have a huge impact on healthcare. In order to effectively manage a variety of diseases, optimised multi-unit floating microspheres are anticipated to give physicians a

new option for a formulation that is more affordable, secure, and bioavailable..These methods also offer enormous prospects for building new controlled and delayed release oral formulations, thereby expanding the horizon of future pharmaceutical discovery. Furthermore, new breakthroughs in pharmaceutical research will undoubtedly present significant opportunities for establishing novel and effective techniques in the creation of these potential drug delivery systems [57].

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