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FLOATING MICROSPHERES – A REVIEW

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Abstract

We address the usage of a controlled drug delivery system with a prolonged GI residence time while talking about drugs with an absorption window in the upper small intestine. Floating drug delivery systems (FDDSs), intended to float on the gastric contents for an extended period, are projected to increase the bioavailability of drugs. Gastro-retentive floating microspheres are low-density systems with sufficient buoyancy to float over the GIT contents and remain there for an extended period of time. The medicine's controlled, delayed release causes a rise in stomach retention and less variation in plasma drug levels. This review paper discusses the anatomy and physiology of the gastrointestinal tract, gastric emptying, mechanism, formulation, and evaluation of floating microspheres.

Keywords: Floating microspheres, gastrointestinal tract, gastric emptying, bioavailability, buoyancy

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INTRODUCTION

The oral route is the most feasible and often-used mode of drug delivery. However, this approach has several physiological drawbacks: the drug-specific absorption window in the upper small intestine, a quick gastrointestinal transit time, and an unpredictable gastric emptying rate.[1] There are several difficulties in designing controlled-release systems for improved absorption and bioavailability. One of these difficulties is limiting the dosage form in the target part of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex process that depends on a number of variables. It is widely acknowledged that how much of the drug is absorbed in the digestive tract depends on how long it is in contact with the small intestinal mucosa.[2] To achieve optimum therapeutic efficiency with the least amount of toxicity and side effects, the medicine must be delivered to the target tissue at the ideal time and in the ideal quantity.[3] A medicinal drug can be delivered to the target area using a variety of methods that allow for a continuous, regulated release. Some of the drawbacks of traditional therapy can be avoided with the use of a well-designed controlled drug delivery system, and the therapeutic potency of a certain medicine can be improved. The use of floating microspheres as medication carriers are one such strategy. In controlled conditions, a microsphere can be utilized to deliver hormones, antibiotics, and other pharmaceuticals. In addition to their fundamental advantages, microspheres can be used in ways that increase their surface area and make it simpler to estimate diffusion and mass transfer properties. Microspheres are tiny granules, typically between 1 and 1000 micrometers in size.[4] Microspheres have advanced technologically to a number of processes, including combinations of phase separations or precipitations, emulsion or solvent evaporation, and spraying techniques.[5] Floating microspheres are one of the most promising methods for buoyant gastro retentive drug delivery.[6] As a result, a delayed transit through the stomach occurs because the preparations for controlled gastrointestinal transit are made to float on gastric fluids with a specific density of less than one.[7] Less variation in plasma drug concentration and improved GI retention result from the drug being released at the desired rate.[8]

ANATOMY AND PHYSIOLOGY OF GIT

It is a prerequisite to understanding the anatomy and physiology of the gastrointestinal tract to study floating drug delivery systems. The stomach is the major part of the digestive system. It is a muscular J-shaped organ in the upper belly.[9] The term "gastrointestinal tract" refers to a continuous muscle tube that extends from the mouth to the anus and is 9 m long (GIT)via a variety of physiological activities like motility, secretion, absorption, digestion, and excretion, it is crucial for absorbing nutrients and getting rid of waste.[10,11] Individual smooth layers carry out the GIT's motor tasks, including intestinal transit and stomach emptying. The stomach, small intestine (duodenum, jejunum, and ileum), and large intestine make up the three main sections of the gastrointestinal tract. There are various layers of tissue that make up the GIT's wall, which runs from the stomach to the large intestine. The "oblique layer" (third muscle layer), which is part of the proximal stomach and contains the stomach, is where the higher parts of the fundus and body emerge.[11] Just behind the diaphragm in the upper left area of the abdomen is where the stomach is situated. The upper abdomen and the left hypochondrium are two of its constituent parts.[11] (Fig.1)

The main functions of the stomach are

- Food storage for a temporary period of 2 hours
- Chyme, acid, and pepsin, which are gradually released into the duodenum, aid in thedigestion of food by helping to break down large molecules like proteins into smaller ones.
- The development of dosage forms that stays in the stomach would be advantageous because the upper small intestine is where drugsare absorbed.

The anatomical regions of the stomach are divided into five types namely cardia, fundus, body or corpus, antrum, and pylorus.

Cardia

Food particles enter the stomach through the cardia, which connects the esophagus and stomach. It is located in the upper part of the stomach, which contains the heart sphincter, preventing food from going back into the esophagus.[10]

Fundus

The dome-shaped muscle that aids in breathing is located near the cardia, right below the diaphragm.[10] The fundus muscle fibers relax to accommodate the rise in volume during feeding. Constant pressure from the fundus forces stomach contents towards the distal stomach. For the chyme (particles) to pass through the pyloric valve and into the small intestine, their size should be between 1-2 mm.[12]

Body or Corpus

This is the stomach's largest and most significant part below the fundus. It serves as a storage space for the body's undigested matter. The stomach contracts in this region, mixing the meal particles.[10,11]

Antrum

The antrum is a pump that is just below the body that employs propulsion to empty the stomach. Until the stomach is ready to transport food particles to the small intestine, it retains food particles. Due to its restricted surface area, absorption is minimal, yet medication transport to the small intestine is hampered.[10,11]

Pylorus

The pyloric sphincter is in the lowest portion of the stomach. Existing stomach contents are managed by a ring-shaped tissue that regulates when and how they move from the stomach to the small intestine.[10]

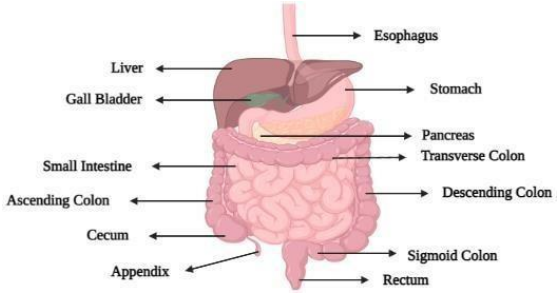

Fig. 1. Anatomy of gastrointestinal tract

GASTRIC EMPTYING

Gastric emptying is process that takes the food to empty from the stomach and enter the small intestine. The gastric emptying rate is controlled by humoral and neural factors. The factors are depth of the antral waves, the pyloric opening, the receptive relaxation of the duodenum, and the type of duodenal contractions. Increasing the frequency of daily meals and reducing the size of each will help alleviate bloating and possibly allow the stomach to empty more quickly. Normal gastric emptying time is 1.5 to 2 hrs after the intake of food. If the gastric emptying time is delayed then it is called gastroparesis. Gastroparesis may cause bacterial overgrowth due to fermentation which hardens the food and cause nausea vomiting and obstruction in the stomach. Diabetes and injury to the vagus nerve due to surgery may produce delayed gastric emptying time.[13]

Wilson and Washington categorize the gastric emptying time into four stages (Fig.2)

Phase I: Fundamental Phase

According to reports, this is a 30- to 60-minute period of rest with infrequent contractions.

Phase II: Pre-Outbreak Phase

It has 20 to 40 minute long intermittent potentials and contractions that can get stronger and occur more frequently as the phase develops.

Phase III: The stage of the outbreak

It comprises 10 to 20 minutes of brief, painful, regular contractions. This stage, which is often referred to as the "housekeeping wave," causes undigested matter to flow from the stomach and into the small intestine.

Phase IV: Transition Phase

This phase occurs as two successive cycles between Phase III and Phase I, which may cause a short-lived transitory phase (Phase IV).

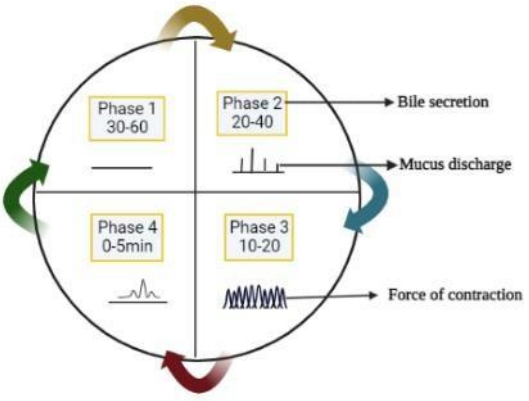

Fig. 2. Phases of Gastric Emptying

FLOATING DRUG DELIVERY SYSTEM

The floating system has a longer buoyancy and lower bulk density than the gastric fluid without influencing gastric emptying in the gastric fluid. In order to increase gastric residence time and control fluctuations in plasma drug concentrations, the drug is gradually released from the system at the predetermined rate, and then the remaining system is emptied from the stomach.[14,15] Drugs that are poorly soluble or unstable in the intestinal fluid are appropriate for floatation systems.[16] To promote gastric retention, floatation devices, and bioadhesive drug delivery systems are two extensively employed strategies. Since the floating system has no adverse effects on the mobility of GIT, it was especially researched.[8]

To keep dosage forms buoyant on food surfaces, little gastric content is needed.[17]

Ideal Characteristics

- Specific gravity must be lower than stomach contents (1.0004–1.01 g/cm3)
- It should release its contents as a reservoir
- A cohesive gel barrier must be formed[18]

Including low-density material or enclosing air will produce low density.[19] Individual units floating can result in issues like sticking together or choking in GIT, which can irritate the stomach. It has been demonstrated that multi-unit floatation systems lessen the inter- and intra-subject accessibility of drug absorption and reduce the possibility of dose dumping.[20]

Two different methods were used to create the FDDS, both of which were based on the mechanism of the buoyancy system.[21] They are,

- Effervescent system
- Non-effervescent system

Floating microspheres come under the non-effervescent system. Systems for non-effervescent buoyant drug delivery rely on the bioadhesion of a polymer to the mucosal layer of the gastrointestinal tract.[22] Polysaccharides, swellable cellulose hydrocolloids, and matrix-forming polymers such as polycarbonates, polyacrylates, polymethacrylates, and polystyrene make up non-effervescent floating dosage forms.[22,23] The drug is combined with a polymer that, when in contact with stomach fluid, expands and retains relative shape integrity while having a lower bulk density than the outer gel-like barrier.[11]

FLOATING MICROSPHERES

Non-effervescent gastro retentive drug delivery systems include floating microspheres. Microspheres that float are also referred to as buoyant particles, hollow microspheres, or microspheres. Non-nucleated hollow spherical particles with a diameter of fewer than 200 micrometers make up levitating microbeads.[24] With the distinct advantages of multi-unit systems as a result of the core cavity, it shows gastro-retentive controlled release distribution with improved bioavailability and is anticipated to be one of the most promising floatation systems. Excellent floatation characteristics within microspheres happened.[24,25] The drug is dissolved or dispersed throughout the particle-matrix using solid biodegradable microspheres, making controlled drug release possible.[26] (Fig.3)

To fabricate drug-filled hollow microspheres or microspheres in various polymeric layers, simple solvent evaporation or solvent diffusion method can be used. This led to hollow cores that dramatically increase the GRT of dosage forms.[23] These systems are frequently produced using polymers including cellulose acetate, Eudragit, calcium alginate, agar, and polycarbonate, low methoxylated pectin.[11] The organic solvent dissolves or disperses the polymer, and the polymer solution dissolves or disperses the drug. A drug solution is homogenized by an aqueous medium containing a polymer to create an oil-in-water emulsion. The organic solvent is subsequently evaporated by raising the temperature under pressure or by continuous stirring.[27]

The formulation solvent, the amount of polymer utilized, and the plasticizer-to-polymer ratio all have an impact on the buoyancy and drug release of the dosage form.[18,28] The microballoons floated continuously over the surface of an acidic dissolving fluid containing surfactant for more than 12 hours.[29]

This approach is not designed to handle drugs that irritate the gastric mucosa, absorb through the GIT, undergo first-pass metabolism, are unstable in the acidic environment of the stomach, or have problems with gastric solubility.[11]

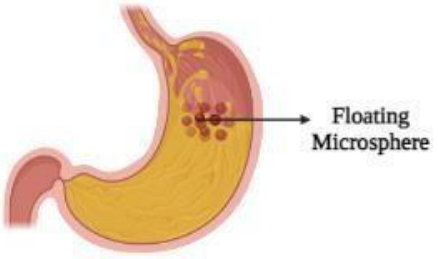

Fig. 3. Floating microspheres

Advantages[30-36]

- Extended time above the minimum effective concentration
- Enhances the bioavailability of drugs that are metabolized in the upper gastrointestinal tract.
- It aids in overcoming the drawbacks of traditional systems of gastric emptying time and residence times.
- Negative side effects can be minimized or completely avoided by delivering the active substance to the site of action.
- There is no chance of dose dumping because floating microspheres in multiple unit dosage forms release the drug uniformly.
- Reduced inter- and intra- subject variability.
- Enhanced patient compliance by loweringthe frequency of dosing.
- Fast absorption results in healthy blood circulation, which is attained.
- Overcome GRT and GET physiological restrictions without altering healthy physiology.
- Even at the alkaline pH of the colon, the floating dose form is entirely absorbed while still in solution.

Disadvantages[30-38]

- Unfavorable conditions for gastric retention - For instance, some extended-release medications should not be used because they may irritate the stomach mucosa or they may become unstable in an acidic environment or they are not among the medications formulated in GRDDS. Aspirin and NSAIDs may also induce gastric lesions.
- Drugs that shouldn't be included in a gastric retention system are those, such as isosorbide dinitrate
- Drugs with GI tract solubility or stability concerns are not suited for floatation devices.
- Drugs must float and function effectively in the stomach, which requires a lot of fluid.
- The size of the drug delivery system expanding during several doses can result in gastrointestinal risks and long-term retention in the stomach.
- As you lie down or sleep, floating formulations soon come off. Patients should refrain from taking the active dosage form right before bed because of this.

Mechanism of Floating Microspheres

As microspheres come into contact with stomach fluid, gel formers, polysaccharides, and polymers hydrate to create a colloidal gel barrier. This barrier then controls the rate of fluid penetration into the device and subsequent drug release.[13,39] As the outermost surface dissolves, the adjacent hydrocolloid layer hydrates, maintaining the gel layer of the dosage form. The air held by the expanded polymer gives the microspheres buoyancy and lowers their density at the same time. Also, minimum stomach content is necessary for proper buoyancy to be achieved. Newer innovations include hollow microspheres made of acrylic resins, cellulose acetate, eudragit, cellulose acetate, and polyethylene oxide, as well as polystyrene floatable shells, gelucire floating granules, polycarbonate floating balloons, and more.

METHODS OF PREPARATION OF FLOATING MICROSPHERES

Solvent Evaporation Technique

The drug and polymer were first dissolved in an organic solvent in a variety of ratios, and at the maintained temperature, the mixture is poured into the solution (room temperature). The homogenous solution is stirred using a magnetic stirrer until the volatile solvent gets evaporated.[40-42] The residue (microspheres) is next filtered and washed with the mixture was then agitated at room temperature to create a homogeneous solution. At the appropriate solvent. Let it about 24 hours to dry before storing it in the desiccator. (Fig.4)

- Polymers: HPMC, Carbopol 940, Ethylcellulose, K4M
- Organic solvents: Acetone, n-hexane, Methylene Chloride
- Lubricants: Liquid paraffin
- Emulsifier: Tween 80

Floating microspheres of losartan can be prepared by using HPMC K100 and sodium alginate, ciprofloxacin with cellulose acetate, rabeprazole with HPMC K15M, and ethyl cellulose, ranitidine with carbopol 934 and chitosan.[43-46]

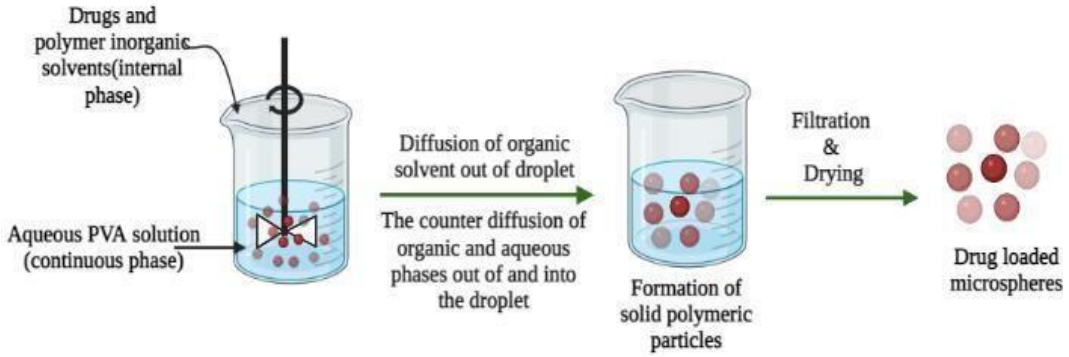

Fig. 4. Solvent evaporation technique

Ionotropic gelation method

In the ionotropic gelation process, the polyelectrolytic solution was dropped into the counter ion solution using a magnetic stirrer to form a hydrogel bead. These hydrogel beads are produced by adding a drug polymeric solution to an aqueous solution that contains several polyvalent cations. In the drug-loaded polymeric droplets, the cations spread and create an ionically crosslinked three-dimensional lattice. (Fig.5)

Temperature, pH of the crosslinking solution, the concentration of drugs, and gas-producing agents are a few variables that affect the ionotropic gelation process.

Polyelectrolyte complexation, ionotropic gelation in a high voltage electrostatic field, emulsion-internal ionotropic gelation, ionotropic gelation followed by coacervation, multi-polyelectrolyte gelispheres, and ionotropic gelation followed by compression are some of the techniques used in the advancement of ionotropic gelation.[47-52]

Amoxicillin trihydrate, a penicillinase-resistant antibiotic which inhibits the formation of the bacterial cell wall can be prepared as floating microspheres with the help of HPMC K4M, Carbopol 934, and sodium alginate with calcium chloride. This facilitates quicker and thorough absorption at the end of 12 hrs.

Amoxicillin trihydrate - Amoxicillin is a penicillinase-resistant antibiotic, like ampicillin. Amoxicillin inhibits the formation of bacterial cell wallsat a particular stage in the process. The Gastrointestinal tract facilitates a quicker and more thorough absorption of the medication. At the end of 12 hours, the microsphere buoyancypercentage ranged from 60 to 90%, indicating improved therapeutic bioavailability.[48]

Lafutidine can be prepared by using HPMC K4M, ethylcellulose, and sodium alginate.[50] Diacerein can be prepared by using sodium alginate, chitosan, and calcium chloride.[51] Famotidine can be prepared by using sodium alginate, HPMC K100, and guar gum.[52]

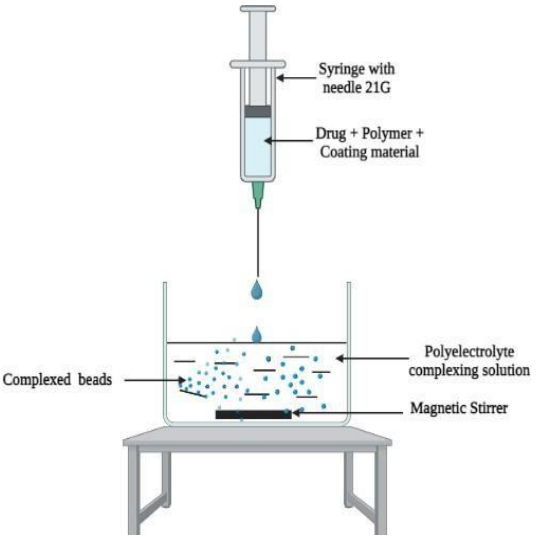

Fig. 5. Ionotropic gelation technique

Emulsion Solvent Diffusion Method

To create a homogeneous solution, the drug and polymer are dissolved in organic solvents before being put into water containing a non-ionic surfactant and organic solvent. The mixture is agitated for approximately 1 hour at a specific rpm to allow the volatile oil to evaporate from the mixture. The mixture is then dried at room temperature after being filtered to remove the microspheres.[53-56] (Fig.6)

- Polymers: HPMC, Ethyl cellulose
- Organic solvents: Ethanol, n-hexane, Dichloromethane
- Non-ionic surfactant: Tween 80

Nizatidine floating microspheres can be prepared by using HPMC, MCC, and polyethylene glycol.[57] Atenolol floating microspheres can be prepared by using ethyl cellulose, eudragit S100.[58] Roxatidine floating microspheres can be prepared by ethylcellulose, HPMC K4M, and HPMC K15.[53]

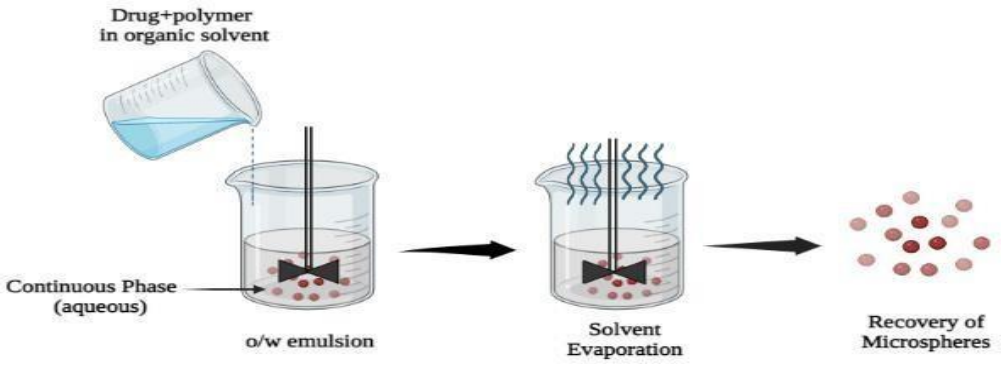

Fig. 6. Emulsion solvent diffusion method

Single Emulsion Technique

This method creates natural polymer microparticulate carriers. In an aqueous medium, the natural polymers are first dissolved, and then they are dispersed in a non-aqueous medium.[59-62] The cross-linking can then be done using either heat or chemical linkers. Crosslinking by heat is affected by adding the dispersion to a previously heated non-aqueous medium. (Fig.7)

Heat denaturation is not suitable for thermolabile drugs.

- Natural polymers - Protein, Carbohydrates
- Chemical cross-linking - Glutaraldehyde, Formaldehyde, Ter phthaloyl chloride, diacid chloride, etc.

Cinaciguat and Daidzein floating microspheres can be prepared by using PLGA and polyvinyl alcohol respectively.[63,64]

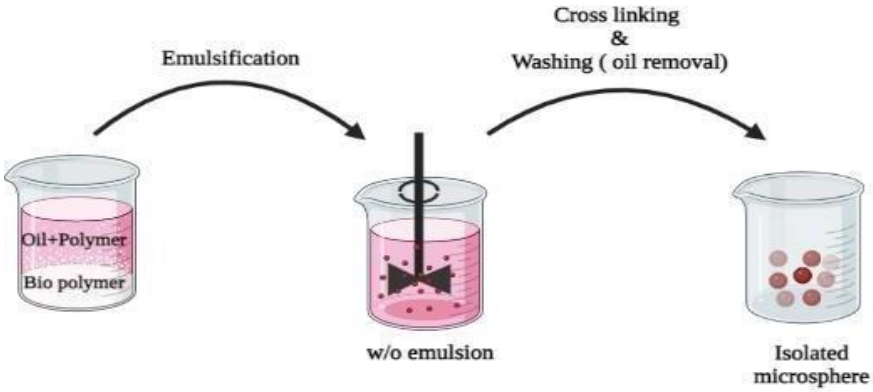

Fig. 7. Single emulsion technique

Double Emulsion Technique

This technique produces double or more emulsions, such as w/o/w. Eventually, the continuous process that uses polymer solution envelopes the drug. First, the emulsion is formed. The formed emulsion is subjected to homogenization before being added to the aqueous solution to create the primary

emulsion. The double emulsion is created as a result.[65,66] The next step is to remove the solvent from the emulsion, either using solvent extraction or solvent evaporation. (Fig.8)

Hydrophilic medications including vaccines, protein/peptides, and conventional drugs can be formulated by using the double emulsion technique. Polymers used may be natural or synthetic.

Atazanavir sulfate floating microspheres can be prepared by using ethyl cellulose, HPMC, and Eudragit E100.[67] Imatinib is prepared by using the PLGA polymer.[68] Zidovudine floating microspheres can be prepared by using ethyl cellulose.[69]

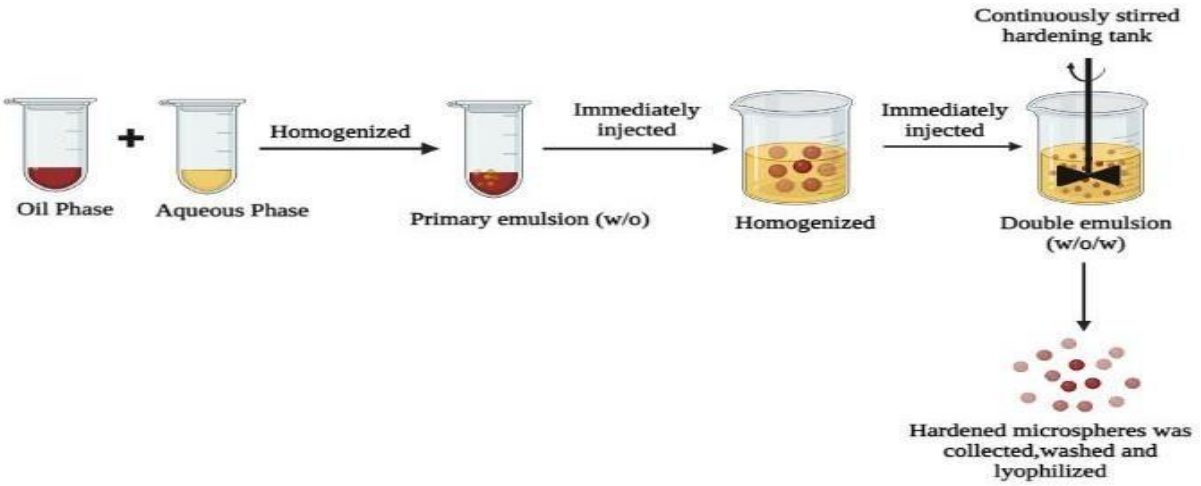

Fig. 8. Double emulsion technique

Spray Drying Technique

To create the slurry, the polymers are combined with the appropriate organic solvent. The drug is added to the polymer solution, stirred thoroughly, and then the mixture is allowed to enter the air-filled chamber with compressed and heated air. The solvent is fed into the heated air chamber through a spray nozzle for evaporation. The cyclone separator separates the microspheres from the moving air once the solvent has evaporated. The microspheres are then gathered. (Fig.9). Polymers like alginate, chitosan, and organic solvents dichloromethane and acetone can be used.[70]

Amoxicillin and felodipine floating microspheres can be prepared by using the polymers chitosan and sodium alginate respectively.[71,72]

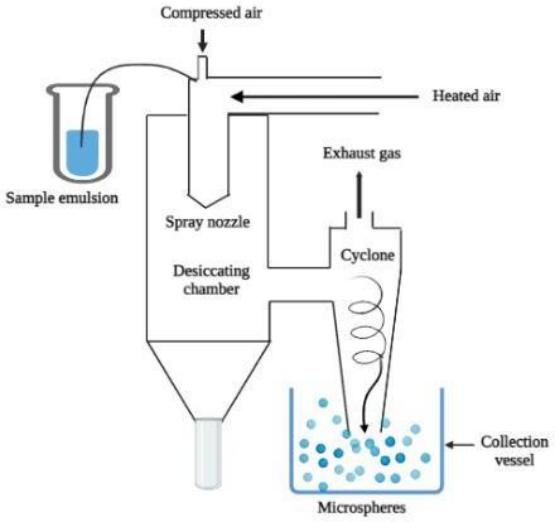

Fig. 9. Spray drying technique

EVALUATION OF FLOATING MICROSPHERES

The floating microspheres are evaluated for various tests like particle size, bulk density, tapped density, compressibility index, Hausner's ratio, percentage yield, floating behavior, *invitro* buoyancy, etc.[73-75]

Floating behavior, in vitro buoyancy, and swelling tests are specific for floating dosage forms.

Floating or Buoyancy test

The time taken for the introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time at which the dosage form remains buoyant is measured. The time taken for the dosage form to come on the surface of the simulated gastric fluid medium is called floating or buoyancy lag time. The total duration of time by which the dosage form floats is called total floating time.

Swelling study

The swelling study of a dosage form can be measured by studying its weight gain or water uptake. It can be measured in terms of percent weight gain.[76]

CONCLUSION

Compared to many other kinds of drug delivery systems, floating microspheres are a superior choice for innovative drug delivery systems. It will eventually take center stage in innovative medicine administration by merging a variety of other techniques. Floating microspheres as gastro retentive dosage forms provide precise control of the target drug's release rate to a specific location, which has a significant impact on health care. These drug delivery systems enable the creation of innovative controlled and delayed release gastrointestinal formulations, further advancing pharmaceutical research and development.

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