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FLOATING MICROSPHERE AS GASTRO RETENTIVE DRUG DELIVERY SYSTEM: AN UPDATED REVIEW

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ABSTRACT

Floating drug delivery system is anticipated to float in long lasting way when come in contact with the gastric contents and subsequently to improve the drugs bioavailability. The different floating formulations which include powders, tablets, pills, capsules, granules and films are presently under research and development. Floating microspheres (FMs) are particularly getting importance because of their varied applicability for drug targeting to stomach. These gastro retentive FMs are systems having less density have the potential to float and distributed evenly through the entire gastric fluid, lessen the chances of gastric emptying and ensure the drug release for longer period of time. The FMs also enhances the patient compliance by diminishing the frequency of dosage. By employing FMs, significant therapeutic effect could be attained from drugs having short half-life. In this review we will discuss fundamentals of floating microspheres along with recent applications of floating microspheres.

Keywords: Gastric retention, Porous carriers, Microballons, Solvent evaporation technique, Sustained drug delivery.

INTRODUCTION

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. Different methodologies have been employed to enhance the of oral dosage forms retention 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.

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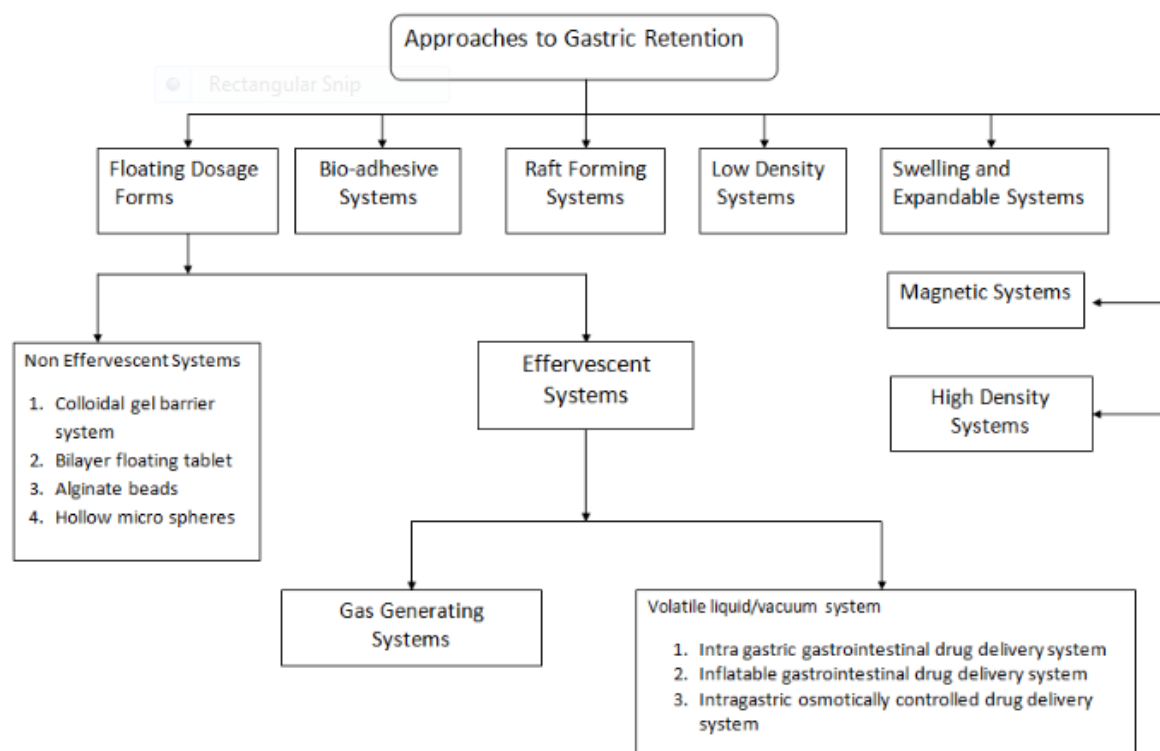


Figure 1: Different approaches for gastric retention

Floating drug delivery systems:

Floating drug delivery systems are systems having low-density that have adequate buoyancy to float over the gastric contents and persist in the stomach environment for an extended period of time. The drug is released gradually at the chosen rate, when the fabricated system floats on the gastric contents resulting enhanced gastric retention time and declines the plasma drug concentration fluctuation.¹

Classification of floating drug delivery system²: There are mainly two systems which are classified below:

Effervescent systems

- Volatile liquid containing systems
- Gas generating systems

Non effervescent systems

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

Benefits of FMs³:

- 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 decrease 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

Demerits of FMs⁴:

- 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.

Polymers Employed for FMs⁵:

Various biodegradable and nonbiodegradable polymers have been examined for FMs formulation. These polymers are from natural, synthetic and semi synthetic origin. FMs 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

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.

Method of Preparation of Floating Microspheres:

Wide ranges of developmental techniques are available for the preparation of Gastroretentive floating microspheres. However, solvent evaporation technique and ionotropic gelation method have been extensively employed by large number of scientific investigators worldwide to explore the different vistas of floating microspheres. During the preparation of floating controlled release microspheres, the choice of optimal method has utmost relevance for the efficient entrapment of active constituents. Selection of fabrication technique generally depends upon the nature of the polymer, the drug, and their intended use.

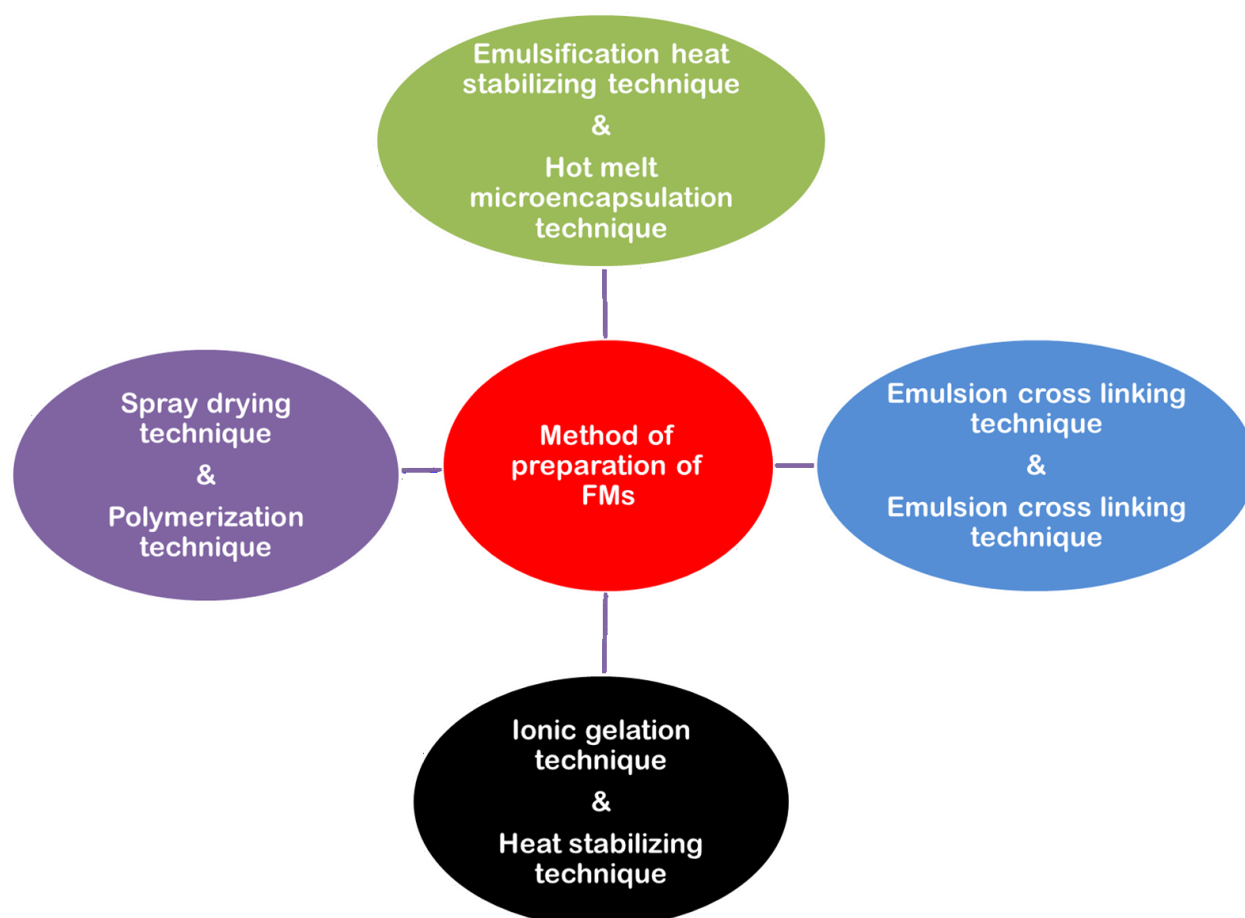


Figure 2: Various method of preparation of FMs

1. Solvent Evaporation Technique:

This technique is widely employed by large number of pharmaceutical industries to obtain the controlled release of drug. This approach involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilization.⁶

2. Oil-In-Water Emulsion Solvent Evaporation Technique:

In this process, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer. In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. Solvent removal from embryonic microspheres determines the size and morphology of the microspheres. It has been reported that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the o/w interface. This leads to the formation of cavity in microspheres, thus making them hollow to impart the floating properties. Oil-in-water emulsion is widely used than water-in-oil due to simplicity of the process and easy cleans up requirement for the final product.⁷

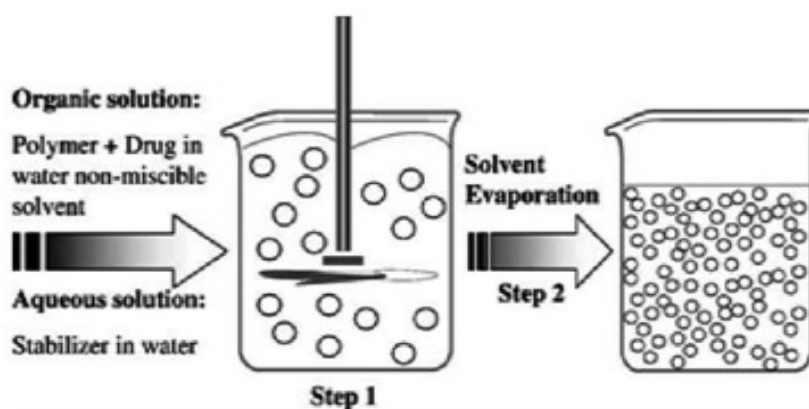


Figure 3: Solvent evaporation method

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.⁸

4. Ionotropic Gelation Method:

In this method, cross linking of the polyelectrolyte takes place in the presence of counter ions to form gel matrix. This technique has been generally employed for the encapsulation of large number of drugs. Polyelectrolyte such as sodium alginate having a property of coating on the drug core and acts as release rate retardant contains certain anions in their chemical structure. These anions forms meshwork structure by combining with polyvalent cations and induced gelation. Microspheres are prepared by dropping drug loaded polymeric solution using syringe into the aqueous solution of polyvalent cations.⁹

Characterization of Floating Microsphere:

Particle size analysis:

The optical microscopy and sieving method is employed to determine the particle size of FMs. The calibrated ocular micrometer is used to examine the mean particle size.¹⁰

Drug entrapment efficiency:

The efficiency of FMs for drug entrapment is evaluated by dividing practical drug content from theoretical drug content.¹¹

Percentage yield:

It is calculated by dividing the total weight of formulated microspheres with weight of excipient along with drug which is multiplied by 100.¹²

It is calculated by:

% Yield: = Weight of hollow microspheres x 100 / Weight of drug taken + total polymer weight

Surface morphology:

The scanning electron microscopy is employed to determine the surface characteristic of FMs. Before evaluation samples of FMs kept under vacuum coated with gold. The internal and external morphology of FMs are determined by this technique.¹³

Floating behavior:

The USP type II apparatus is employed to determine the floating behavior of FMs. The microspheres kept into the apparatus in gastric fluid having pH 1.2, temp 37±0.5°C. It is calculated by¹⁴:

$$\text{Buoyancy (\%)} = \frac{Q_f}{Q_s + Q_f} \times 100$$

Q_f = Mass of FMs, Q_s = Mass of hollow microsphere

Swelling ratio:

Swelling property of floating microspheres is studied by soaking the known weight of microspheres at 37 ± 0.5°C in 0.1 N HCl or phosphate buffer pH 6.8 in a glass beaker for the required period of time. The microspheres are allowed to swell and removed at different time intervals.¹⁵

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.¹⁶

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.¹⁷

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.¹⁸

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.¹⁹

Recent Advancement of Gastro Retentive Floating Microspheres:

Nila *et al* developed sustained release gastro retentive FM 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 (11). Abbas *et al* developed FM 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 FM-ENA exhibited excellent entrapment efficiency of drug, good buoyancy and significant % yield. The investigators concluded that fabricated FM have the potential to deliver the drug in controlled manner and also enhance the patient compliance (9). Gupta *et al* formulated and evaluated silymarin (SLM) FM to enhance the bioavailability of drug and increase the gastric residence time. The researchers revealed that fabricated FM-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 FM-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) FM with the help of ionotropic gelation and solvent evaporation approach employing various polymers such as chitosan, Carbopol and sodium alginate. The researchers showed that FM 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 $97.56 \pm 0.87\%$. 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.²²

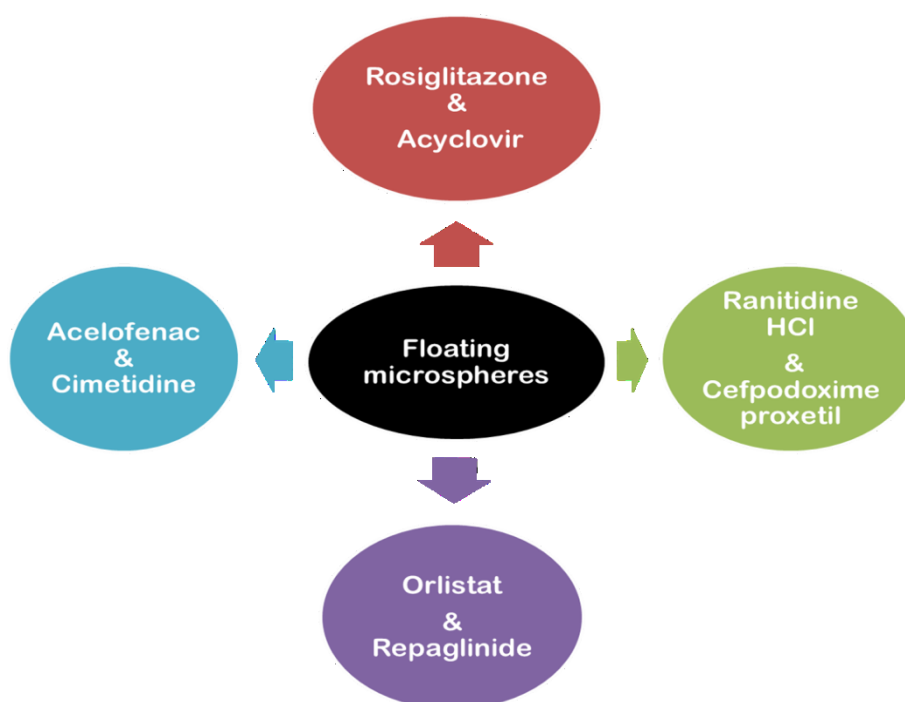


Figure 4: Drugs formulated as floating microspheres

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Floating microspheres as gastroretentive dosage forms precisely control the release rate of target drug to a specific site and facilitates an enormous impact on health care. Optimized multi-unit floating microspheres are expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the effective management of diverse diseases. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

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