Review Article

A REVIEW ON FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEM – A NOVEL APPROACH TO GASTRIC RETENTION

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ABSTRACT

Well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using multiparticulate as carriers for drugs. The purpose of writing this review on method of prepare floating multiparticulate is to compile the recent literature with special focus on the classification and formulation aspects, principal mechanism of floatation to achieve gastric retention, characterization of floating multiparticulate system.

Keywords: Floating system, Multiparticulate system, gastric retention.

INTRODUCTION

Conventional oral dosage forms offer no control over drug delivery, leading to fluctuations in plasma drug level. These have a disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. Various approaches have been worked out to improve the retention of oral dosage form in the stomach, e.g. floating systems, swelling and expanding systems, bioadhesive systems and high density systems[1].

Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres[2,3].

Over the last three decades, various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time. High-density systems having density of ~3 g/cm are retained in the rugae of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm^3. Swelling systems are capable of swelling to a size that prevents their passage through the pylorus; as a result, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swells[4-6]. Bio/mucoadhesive systems[7] to the gastric epithelial cell surface or mucin and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The epithelial adhesive properties of mucin have been applied in the development of Gastro retentive drug delivery systems. Floating system[8] first described by Davis (1968), are low-density systems[9] that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration[10,11].

Floating multiparticulate are gastro-retentive drug delivery systems based on non-effervescent and effervescent approach. Hollow microspheres 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 200 micrometer[12].

FACTORS AFFECTING THE GASTRIC EMPTYING

1. Density, size and shape of the dosage form[12-14].
2. Concomitant ingestion of the food and its nature, caloric content and frequency of intake[15,16].
3. (Simultaneous) administration of drugs acting as anticholinergic agent (e.g. Atropine, Propentheline), opoides (e.g. Codeine) and prokinetic agents (e.g. Metoclopromide, Isapride)[17].
4. Biological factor such as gender, posture, age, sleep, body weight, physical activity and disease states (e.g. diabetes, crohn's disease)[18,19].

SUITABLE DRUG CANDIDATES FOR FLOATING GASTRORETENTION

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is

prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need of repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3h[20]. As shown in figure in figure 1 (a) and (b).

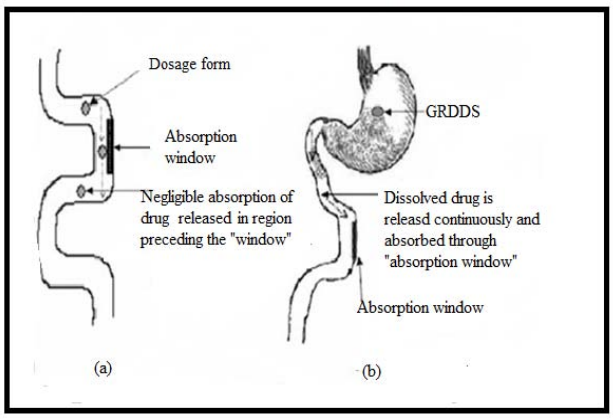

Figure 1: Drug absorption in the case of

(a) Conventional dosage forms

(b) Gastroretentive drug delivery systems

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

i) Narrow absorption window in GI tract, e.g., Riboflavin in a vitamin Deficiency and Levodopa.

ii) Primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Scinnarazine.

iii) Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.

iv) Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.

v) Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate.

A FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEM

In recent years, multiparticulate dosage form as matrix or coated pellets or micro particles have gained popularity for variety of reasons. Considerable research efforts have been taken on oral sustained or controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage form. Currently more emphasis is given on floating concept of multiparticulate reservoir type delivery system. Floating multiparticulate oral sustained release drug delivery system include hollow microspheres (micro balloons), low density floating micro pellets, floating micro beads (acrylic resin based) etc. Reports have been published on the development of both non-effervescent and effervescent multiple unit systems. Much research has been focused and the scientists are still exploring the field of hollow microspheres[21,22].

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems are classified depending up on the two formulations variables Effervescent and Non-effervescent systems.

a) Effervescent floating dosage forms

These are the matrix types of systems which are prepared by using swellable like methyl cellulose, HPMC and chitosan based polymers as well as various effervescent compounds like Sodium carbonate, Calcium carbonate, Tartaric acid and Citric acid. They are formulated in such a way that when in contact with the acidic gastric contents liberation of CO_2 takes place and gets entrapped in to the swollen hydrocolloids which provides buoyancy to the dosage forms such as Famotidine[23], Amlodipine besylate[24] which is shown in figure no 2 (a).

b) Non effervescent floating dosage form

These dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix forming polymers like polycarbonates, polymetha acrylate and polystyrene[25]. The formulation is done by mixing the drug and the gel-forming hydrocolloid, after oral administration of this dosage form swells while in contact with gastric fluids attains bulk density of <1. The buoyancy of dosage form was attained due to the air entrapment in to the swollen gel like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass[26] Drugs such as Famotidine[27], Levodopa[28] which is shown in figure no. 2 (b).

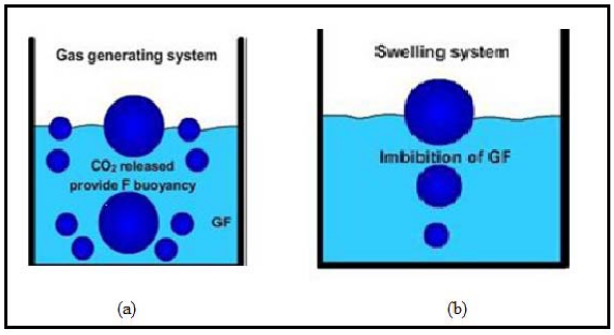

Figure 2: (a) Effervescent Systems (b) Swelling Floating System

METHODS OF PREPARATION OF FLOATING MULTIPARTICULATE SYSTEM

1) Solvent evaporation method

Floating multiparticulate dosage form was prepared by solvent diffusion and evaporation methods to create the hollow inner core. 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 Polyvinyl alcohol 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[30,31]. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties[32,33]. The polymers studied for the development of such systems include Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide and Polycarbonates.

Furthermore, a novel multi-particulate gastroretentive drug delivery system based on low-density foam powder has been proposed and its performance demonstrated *in-vitro*[34]. Floating microparticles consisting of Polypropylene foam powder, Verapamil HCl (as the model drug) and Eudragit RS, Ethylcellulose or Poly (methyl methacrylate) (PMMA) were prepared with an oil-in-water solvent extraction/evaporation method (Figure no. 3a). The drug and release-rate-controlling polymer were dissolved in Methylene chloride. Polypropylene foam powder was then dispersed within this organic phase. The resulting suspension was subsequently emulsified into an external aqueous Poly (vinyl alcohol) solution and agitated with a stirrer to allow microparticle formation. The microparticles were separated by being sieved, washed with water and dried in a desiccator; they were irregular in shape and highly porous. Importantly, the drug encapsulation efficiency was high and almost independent of the theoretical loading of the system. In all cases, good *in-vitro* floating behavior was observed. Interestingly, a broad spectrum of release patterns could be obtained with the investigated formulations.

Further studies focused on the development of an improved preparation method for this type of low-density, foam-based, floating microparticle and also on the demonstration of the system's performances *in-vitro*[35]. Major advantages of the suggested novel preparation technique include short processing times, no exposure of the ingredients to high temperatures, the ability to avoid toxic organic solvents and high encapsulation efficiencies (close to 100%). Floating microparticles consisting of Polypropylene foam powder, model drug (Chlorpheniramine maleate, Diltiazem HCl, Theophylline or Verapamil HCl) and a second polymer [Eudragit RS or Poly(methyl methacrylate)] were prepared by soaking microporous foam particles with an organic solution of the drug and polymer and subsequent drying (Figure 3b)[36]. Good *in- vitro* floating behavior was observed in most cases and a broad variety of drug release patterns could be achieved by varying the drug loading and type of second polymer. In addition, the low-density microparticles could be compressed into rapidly disintegrating tablets, providing an easily administrable oral dosage form[37].

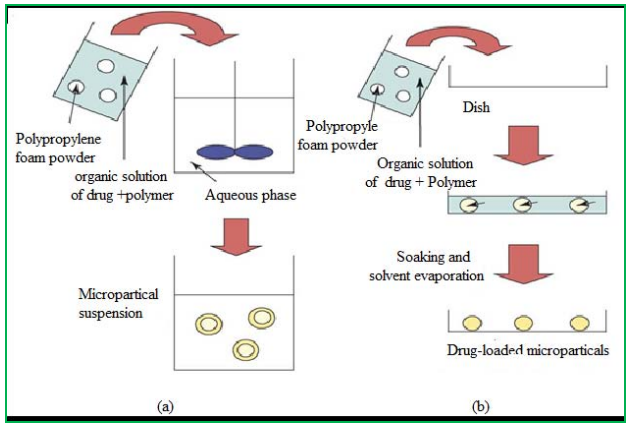

Figure 3: Schematic presentation of the preparation of floating microparticles based on low-density foam powder, using (a) The solvent evaporation method or (b) The soaking method.

2) Ionotropic gelation method

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form beads. Since, the use of Alginates, Gellan gum, Chitosan and Carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose[38]. The natural polyelectrolytes inspite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. Biomolecules can also be loaded into these beads under mild conditions to retain their three dimensional structure[39]. The schematic representation of ionotropic gelation method is shown in figure 4.

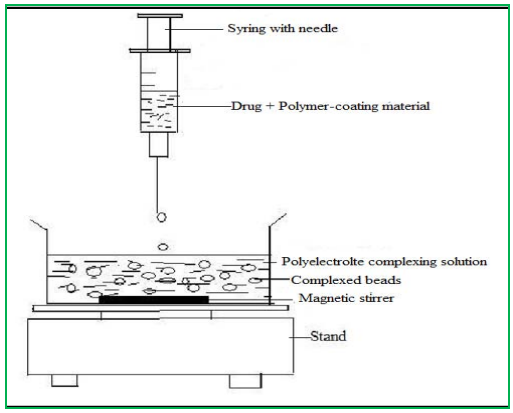

Figure 4: Ionotropic gelation method

El-Gibaly et al[40] developed floating (F) microcapsules containing melatonin (MT), prepared by the ionic interaction of Chitosan and negatively charged surfactant, Sodium dioctyl sulfosuccinate (DOS). The characteristics of the floating microcapsules generated compared with the conventional non-floating (NF) microspheres manufactured from Chitosan and Sodium tripolyphosphate (TPP) were also investigated.

Talukder, R. et al[41] developed floatable multiparticulate system with potential for intra gastric sustained drug delivery. Cross-linked beads were made by using calcium and low methoxylated pectin (LMP), which are an anionic polysaccharide, Calcium, LMP and Sodium alginate. Beads were dried separately in an air convection type oven at 40°C for 6 hours and in freeze dryer to evaluate the changes in bead characteristics due to process variability. Riboflavin (B-2), Tetracycline (TCN) and Methotrexate (MTX) were used as model drugs for encapsulation. Ionic and nonionic excipients were added to study their effects on the release profiles of the beads.

3) Emulsion solvent diffusion method

Kawashima and colleagues[42,43] proposed hollow microspheres (so-called 'microballoons') with drug in their outer polymer shell prepared by novel emulsion solvent diffusion method. Based on Eudragit-S (an enteric polymer), containing the drug in the polymeric shell. The preparation procedure and mechanism of microballoon formation is schematically illustrated in Figure no. 5. A solution of polymer and drug in ethanol methylene chloride is poured into an agitated aqueous solution of poly (vinyl alcohol). The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the microparticles.

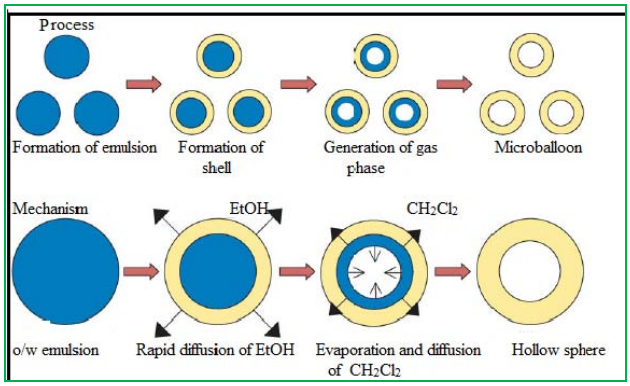

Figure 5: Preparation technique (emulsion-solvent diffusion method) and mechanism of 'microballoon' formation.

CHARACTERIZATION OF THE FLOATING MICROPARTICULATE SYSTEM

The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier[44].

1) Micromeritic properties[45,46].

Angle of Repose[47,48], Density, Hausner's Ratio, compressibility index is determined by using proper equation.

2) Particle size and shape

SEM provides higher resolution in contrast to the LM[49]. The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of multiparticulate. LM provides a control over coating parameters in case of double walled microspheres. The multiparticulate structures can be visualized before and after coating and the change can be measured microscopically. SEM allows investigations of the multiparticular surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy[50] is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the multiparticulate.

3) Capture efficiency

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:

% Entrapment = Actual content/Theoretical content x 100

4) Floating behavior[51]

Appropriate quantity of the floating microparticulate was placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0), the mixture was stirred with a magnetic stirrer. The layer of buoyant microparticulate was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Buoyancy (\%)} = Wf / Wf + Ws$$

Where,

Wf and Ws are the weights of the floating and settled microparticles

5) *in-vitro* release studies[52,53]

The release rate of floating microparticulate was determined in dissolution apparatus. A weighed amount of floating microspheres equivalent to Dose of drug is taken and placed in the basket of dissolution rate apparatus. The dissolution fluid was maintained at 37 ± 1°C at a rotation speed. Perfect sink conditions prevailed during the drug release study.

6) *in-vivo* studies

The *in-vivo* floating behavior can be investigated by X-ray photography of hollow microparticulate loaded with barium sulphate in the stomach of beagle dogs. The *in-vitro* drug release studies are performed in a dissolution test in a dissolution media. The *in-vivo* plasma profile can be obtained by performing the study in suitable animal models. The list of floating multiparticulate marketed preparation as shown in table 1.

THE ADVANTAGES OF FLOATING MICROPARTICULATE[54]

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
3. Better therapeutic effect of short half-life drugs can be achieved.
4. Gastric retention time is increased because of buoyancy.
5. Drug releases in controlled manner for prolonged period[55].
6. Site-specific drug delivery to stomach can be achieved[56].
7. Enhanced absorption of drugs which solubilise only in stomach[57].
8. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
9. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multiparticulate system.

APPLICATIONS OF FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEMS[58]

Floating multiparticulate drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

1) Sustained drug delivery

Hollow microspheres of non-steroidal antinflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quiet beneficial for rheumatic patients[59].

2) 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, eg, Riboflavin and Furosemide. Bilayer-floating capsule was developed for local delivery of Misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs[60].

3) Absorption enhancement

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption[61].

FUTURE SCOPE OF FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEMS

Floating multiparticles can greatly improve the pharmacotherapy of the stomach through local drug release, used to eradicate *Helicobacter pylori* from the sub-mucosal tissue of the stomach most effectively and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis[61].

This system allows administration of non-systemic, controlled release antacid formulation containing Calcium carbonate and also locally acting anti-ulcer drugs (such as Lansoprazole)[61]. In stomach buoyant microparticles are considered as a beneficial strategy for the treatment of gastric and duodenal cancers. Floating multiparticulate systems may be used as a carrier for the drugs having narrow absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are absorbed only from very specific regions of GI tract. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as Calcitonin, Erythropoietin, Vasopressin, Insulin, low molecular weight Heparin and LHRH. Floating microparticals of NSAIDs are very effective for reducing their major side effect, gastric irritation as well as for controlled release; for example floating microspheres of Indomethacin are quite beneficial for rheumatic patient.

CONCLUSION

Gastro retentive floating multiparticulate have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low

bioavailability and extensive first pass metabolism. The control of gastro intestinal transit could be the focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patient.

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