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A REVIEW ON APPROCHES OF FLOATING MICROBALLONS

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ABSTRACT

Novel drug delivery system as a major advance to solving the problems related to the release of the drug at specific site. In recent years, in oral sustained or controlled release multiparticulate drug delivery system extensive research works have been occurs because of its advantages over monolithic dosage form. Now a day's floating concept of multiparticulate reservoir type delivery system more importance. These systems have several advantages over conventional multi dose therapy. There are various approaches in delivering a therapeutic substance to the target site in a sustained release fashion. One such approach is using microspheres as carriers for drugs. Microencapsulation is used to modify and delay drug release from pharmaceutical dosage forms. Microspheres efficiently utilized in controlled delivery of many drugs but wastage of drug due to low drug entrapment efficiency is the major drawback of such micro-particulate system. This review provides brief information about floating microspheres, method of preparations, evaluation and application of microspheres for sustained drug delivery.

KEYWORDS: Floating,Microspheres,controlled release

INTRODUCTION

Oral sustained release floating multiparticulate drug delivery system include low density floating micro pellets, floating micro beads (acrylic resin based), hollow microspheres (micro balloons) etc. The article published on the development of both effervescent and non-effervescent type of floating drug delivery. Much research has been focused and the scientists are still exploring the field of hollow microspheres.[1]

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Gastroretensive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of
1.Mucoadhesion
2.Flotation
3.Sedimentation
4.Expansion modified shape systems or by the simultaneous administration of pharmacological agent that delay gastric emptying.

Advantages of floating microspheres[16,17]

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances.
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.
6. Site-specific drug delivery to stomach can be achieved.
7. Enhanced absorption of drugs which solubilise only in stomach.
8. Uniform release of the drug.
9. Avoidance of gastric irritation.

Disadvantages

Floating system is not feasible for those drugs that have solubility or stability problem in GIT.

1. These systems require a sufficiently high level of fluids in the stomach for enabling the system to float and to work efficiently.
2. The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo extensive first pass metabolism, may not be suitable for FDDS as the slow gastric emptying limits the systemic bioavailability.
3. Some drugs present in the floating systems cause irritation to gastric mucosa.[18,19,20]

I)APPROCHES FOR GASTRIC RETENTION

Various approaches have been reported to achieve gastric retention of an oral dosage form. These include.

a.Hydrodynamically balanced systems

In hydrodynamically balanced systems, drug with gel-forming hydrocolloids are meant to remain buoyant over the stomach content. This prolongs gastric retention time and maximizes the amount of drug that reaches its absorption sites. These hydrocolloids on contact with gastric fluid, hydrates and forms a colloid gel barrier around its surface.[7]

b.Effervescent systems

The gas generating agents such as carbonates (e.g., sodium bicarbonate) and other organic acid (e.g., citric acid and tartaric acid) are utilized in the formation effervescent systems. The density of the present system is reduced due to the production of carbon dioxide by the reaction of gas generating agents with gastric acid, thus allowing the system to float on the gastric fluid.[8]

C.Low-density systems

Floating systems are based on low density approach. Floating drug delivery systems by virtue of their bulk density lower than gastric fluids (<1 g/ml), float over the gastric fluid and release the drug slowly for a longer period of time. They are prepared by incorporating low-density materials, entrapping oil or air. Most are multiple unit systems and are also called "microballoons" because of their low-density core.[9]

D.Raft systems

Raft systems upon contact with gastric fluid form a viscous cohesive gel, which swells to form a continuous layer called a raft. Generation of CO_2 by a gel forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) makes the raft float on gastric fluid.[10]

E.Bioadhesive or mucoadhesive systems

Bioadhesive systems bind to the gastric epithelial cell surface and extend the residence time of the dosage form in the stomach, thereby facilitating an intimate contact of drug with the biological membrane for prolonged duration. This approach involves the use of bioadhesive polymers such as polycarbophil, carbopol, lectins, chitosan and gliadin.[11]

F.High-density systems

High-density systems have a density (3 g/ml) far exceeding that of normal stomach contents (1 g/ml) and are thus retained in the fold of the stomach for a longer period of time. This is achieved by coating the drug with heavy inert materials such as barium sulfate, zinc oxide, titanium dioxide, iron powder, etc.[12]

Development of Floating Microspheres

Floating microspheres are gastro-retentive drug delivery systems based on non-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. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs.[10,11] 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. When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy.[1,7,11,12] Hollow microspheres of Acrylic resins, Eudragit,

PMAA, Polyethylene oxide, and Cellulose acetate; Polystyrene floatable shells; Polycarbonate floating balloons and Gelucire floating granules are the recent developments. Hollow microspheres are 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.[13,14] 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.[15, 16,17] The polymers studied for the development of such systems include Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Agar, Polyethylene oxide and Polycarbonates.

Mechanism of floating microspheres

The microspheres come to contact with gastric fluid and gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, ethyl cellulose. cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.2

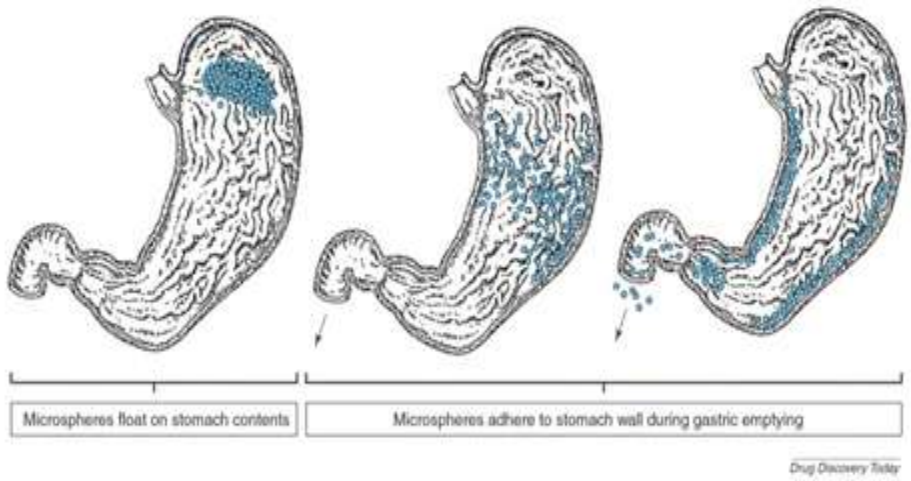

Figure 1: Floating of microspheres in stomach

Methods of preparation of floating microspheres

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[6], 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.[4]

a. Oil-in-oil emulsion solvent evaporation method

During a great number of microencapsulation techniques for the formation of sustained release drug delivery systems, one of the popular methods is the emulsion solvent evaporation method. In order to increase the encapsulation efficiency, a mixed solvent system comprising 1:1 proportions of Acetonitrile and dichloromethane was used as a dispersed phase, and the corn oil was used as a continuous phase. Microspheres containing anti-hypertension drug, Felodipine, were prepared by the emulsion solvent evaporation method (o/o) using Acrylate methacrylate copolymers. The morphology of the microspheres was evaluated using scanning electron microscope, which showed a spherical shape with smooth surface.[5]

b. Foam-based method for floating microparticles

A novel multi-particulate gastro retentive drug delivery system based on low-density foam powder has been proposed in which, 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.[6]

2. Ionotropic gelation method[7,8]

Ionotropic gelation is based on the ability of Polyelectrolytes to cross link in the presence of counterions 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. 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 hydro gel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations.

3. Emulsion solvent diffusion method[5,9]

Kawashima and colleagues[5,6] proposed hollow microspheres 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 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.

Evaluation parameters of floating microspheres

1. Micromeritics properties[12,13]

Floating microspheres are characterized by their micromeritics properties such as particle size, Flow property and Density. Angle of Repose[13,14] Hausner's Ratio, compressibility index is determined by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method. The hollow nature of microspheres is confirmed by scanning electron microscopy.

2. Floating behavior[14]

Appropriate quantity of the floating microspheres were 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.

Buoyancy (%) = Wf / Wf + Ws

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

3.% Drug entrapment[15]

Accurately weighed microspheres were taken, thoroughly triturated and suspended in a minimal amount of solvent. The suspension was filtered to separate shell fragments. Drug contents were analyzed and % Drug entrapment is calculated by using following equation.

% Drug Entrapment= Actual drug content /Theoretical drug content×100

4. *In-vitro* release studies[15]

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 type of dissolution test apparatus. The dissolution fluid was maintained at 37 ± 1°C at a rotation speed. Perfect sink conditions prevailed during the drug release study.

5. *In-vivo* studies[16]

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.

APPLICATIONS

1. Sustained drug delivery

Hydrodynamically balanced system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. These systems have bulk density of <1, as a result of which they can float on the gastric contents.

2. Site specific drug delivery

These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine eg. Riboflavin, Furosemide and Misoprostal.

3. Absorption enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as FDDS, thereby maximizing their absorption.

4. Maintenance of constant blood level

These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.

CONCLUSION

Gastroretentive floating drug delivery technology has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents.Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. 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. Increased sophistication of this technology will ensure the successful advancements in the avenue of gastroretentive microspheres therapy so as to optimize the delivery of molecules in a more efficient manner. 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. 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. Hollow microsphere promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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