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Floating multiparticulate oral sustained release drug delivery system

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ABSTRACT

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving sustained or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. One of the approaches toward this goal is to develop the floating multiparticulates so as to increase the gastric retention time. Such systems have more advantages over the single-unit dosage forms. The development of floating multiparticulates involves different solvent evaporation techniques to create the hollow inner core. In this review, the current status of floating multiparticulate drug delivery systems including hollow microspheres (micro balloons), low density floating micro pellets and floating micro beads (acrylic resin based), microcapsules etc, their evaluation parameter, advantages, application, limitation and future potential for oral sustained release drug delivery are discussed.

Keywords: Floating, Multiparticulates, Microspheres, Microcapsules.

INTRODUCTION

Multiparticulate drug delivery system applies specially to multiple particles such as pellets, beads, microspheres, microcapsules. In recent years, multiparticulate dosage forms or microparticles have gained in popularity for a variety of reasons. Considerable research efforts have been spent on oral sustained or controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage forms[1]. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with

diameter of 0.05-2.00mm. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet[2] (Figure 1).

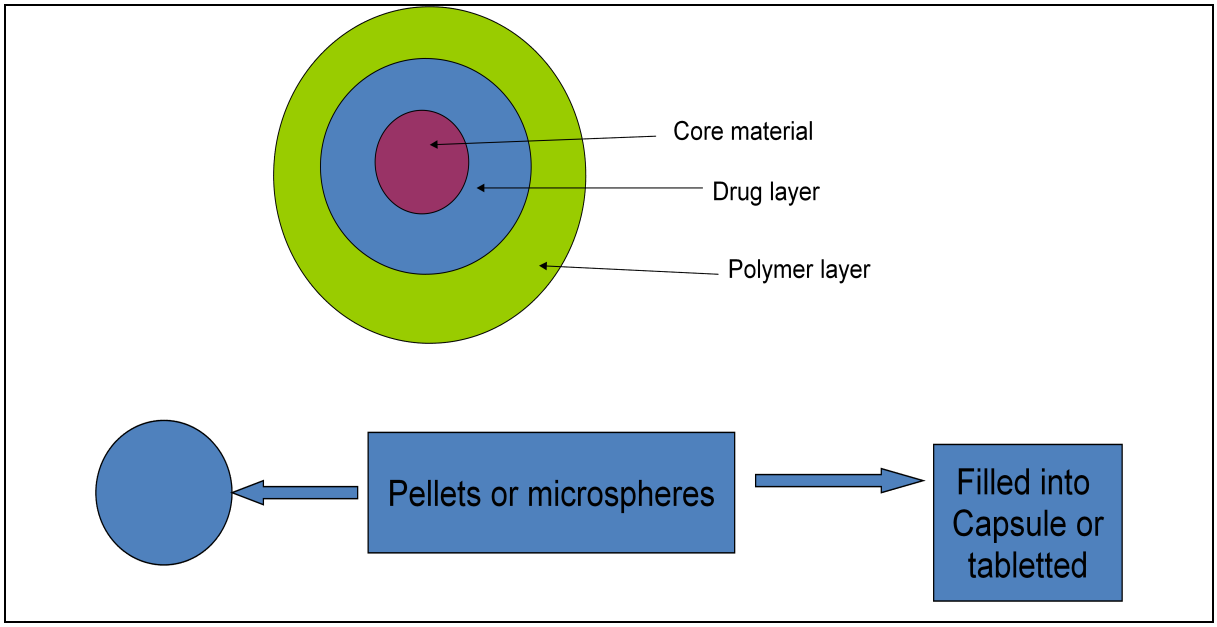

Figure 1: Multiparticulate Drug Delivery Systems

The system is based on the expansion of the core (non effervescent FDDS or low density approach), which lead to floating due to low density. Also the air entrapped by the swollen polymer confers buoyancy to this dosage forms. Floating multiparticulate oral sustained release drug delivery system includes; hollow microspheres (microballoons), low density floating micropellets and Floating microbeads[3].

Multiparticulate carriers (microspheres) are defined as homogeneous, monolithic particles in the size range of about 0.1-1000 µm and are widely used as drug carriers for controlled release. Multiparticulate carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently dosage forms that can precisely control the release rates and target drugs to a specific body site have created enormous impact in formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems. They have varied applications and are prepared using various polymers. However, the success of these microspheres is limited due to their short residence time at the site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling gastroretentive and bioadhesion characteristics to multiparticulates and developing gastroretentive bioadhesive multiparticulates. These multiparticulates have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site[4].

It is stated that, ‘the multiparticulates’ float on the stomach contents, and then adhere to the mucous linings as the stomach empties (Figure 2). The release of drug from the system can be controlled to coincide with the half-life emptying of the system from the stomach[5].

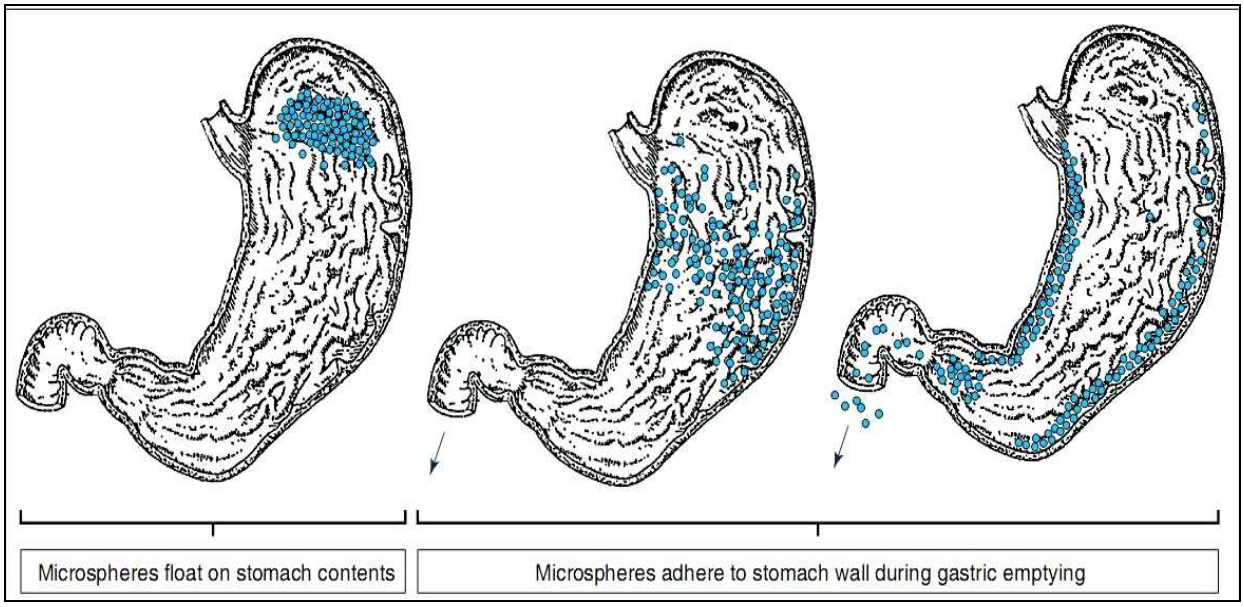

Figure 2: Proposed mechanism for retention of microspheres in the human stomach

The floating multiparticulate oral sustained release drug delivery system have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

Floating multiparticulates drug delivery system has following objects;

- ✓ Sustain release or prolong release medication
- ✓ Taste masking
- ✓ Improve stability
- ✓ Increase solubility or dispersability
- ✓ Increase therapeutic efficiency.

Some approaches to floating multiparticulate formulation

A floating multiparticulate drug delivery system was developed by Jain et al., 2006 who prepared novel calcium silicate based microspheres of repaglinide and investigated in vivo gastro-retentive performance and pharmacokinetic parameters of optimized floating microspheres (RgFMCS4) consisting of (i) calcium silicate (CS) as porous carrier; (ii) repaglinide (Rg), an oral hypoglycemic agent; and (iii) Eudragit S (ES) as polymer. The optimized formulation demonstrated favorable in-vitro-floating and drug release characteristics. The gastroretentive behavior of this optimized formulation was compared with non-floating microspheres (RgNFM) prepared from the identical polymer. The relative bioavailability of Rg loaded floating microspheres was found to be increased about 3.17 times in comparison to that of the marketed tablet. The enhanced bioavailability and eliminated half-lives of Rg formulation observed in the present study are attributed to the floating nature of the designed formulations[6].

- Jain et al., 2006, prepared porous carrier-based floating Orlistat microspheres for gastric delivery using calcium silicate as porous carrier and Eudragit S as polymer by solvent evaporation method. The microspheres were found to be regular in shape and highly porous. Microsphere formulation CS4, containing 200 mg calcium silicate, showed the best floating ability (88% ± 4% buoyancy) in simulated gastric fluid as compared with other formulations. Release pattern of orlistat in simulated gastric fluid from all floating microspheres followed Higuchi matrix model and Peppas- Korsmeyer model. Prolonged gastric residence time of over 6

hours was achieved in all rabbits for calcium silicate based floating microspheres of orlistat. The enhanced elimination half-life observed after pharmacokinetic investigations in the present study is due to the floating nature of the designed formulations[7].

- Patel et al., 2006, developed floating microspheres to obtain prolonged and uniform release in the stomach as once a day formulation. The major advantage of the preparation technique was short processing time, the lack of exposure of the ingredients to high temperature, and high encapsulation efficiencies. In the present study, preparation of metformin hydrochloride floating microspheres, evaluation of floating drug delivery system (FDDS) in vitro, prediction of the release, and optimization of floatation and drug release pattern to match target release profile was investigated. Floating microspheres were prepared by non-aqueous emulsification solvent evaporation technique using ethylcellulose as the rate controlling polymer and metformin hydrochloride as a drug[8].
- Shrivastava et al., 2005, prepared and evaluated floating microspheres of cimetidine as model drug for prolongation of gastric residence time. The microspheres were prepared by the solvent evaporation method using polymers hydroxypropylmethyl cellulose and ethyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. The prepared microspheres exhibited prolonged drug release (8 h) and remained buoyant for > 10 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. In vitro drug release studies were performed and drug release kinetics was evaluated using the linear regression method. In vitro studies demonstrated diffusion-controlled drug release from the microspheres[9].
- Streubel et al., 2002, developed floating microparticles composed of polypropylene foam, Eudragit S, ethyl cellulose (EC), and polymethyl metha acrylate (PMMA) and were prepared by solvent evaporation technique. High encapsulation efficiencies were observed and were independent of the theoretical drug loading. Good floating behavior was observed as more than 83% of microparticles were floating for at least 8 hr. The in vitro drug release was dependent upon the type of polymer used. At similar drug loading the release rates increased in the following order PMMA < EC < Eudragit S. This could be depending to the different permeability of the drug in these polymers and the drug distribution within the system [10].
- Stithit et al., 1998, developed buoyant theophylline microspheres for use as buoyant reservoir with increased retention time in stomach. A polymer mixture of cellulose acetate butyrate and Eudragit RL 100 (1:1) was used. The drug polymer dispersion was pressurized under carbon dioxide gas, which dissolved in the drug polymer dispersion and formed bubbles upon release of pressure. Some of the bubbles were entrapped in the dispersed drug polymer droplets and eventually formed internal cavities in microspheres[11].
- Thanoo et al., 1993, has developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids as evidenced by scanning electron microscopy (SEM). It has been high drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug-to-polymer ratio increased both their mean particle size and release rate of drug[12].
- Kawashima et al., 1991, prepared multiple-unit hollow microspheres by emulsion solvent diffusion technique. Drug and acrylic acid polymer were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer-to-drug ratio. Microballoons were floatable in vitro for 12 hr when immersed in aqueous media. Radiographical studies proved that microballoons orally administered to humans were dispersed in the upper part of stomach and retained there for 3 hr against peristaltic movements[13].

- Joseph et al., 2002, developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. In vivo studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was carried out from plasma concentration vs. time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times than that of the free drug and 4.8 times than that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period [14].
- Soppinath et al., 2001, prepared hollow microspheres of cellulose acetate containing cardiovascular drugs, by novel solvent diffusion-evaporation method. The method involves organic solvents such as acetone and ethyl acetate. Because of solubility, the organic solvents diffuse into the aqueous phase; this process is responsible for the induction of interfacial polymer deposition resulting in the formation of hollow microspheres .Scanning electron microscopic studies indicated the hollowness and absence of drug crystals on the surface of microspheres suggesting uniform drug distribution, as the physical state of the drug influences the drug release kinetics. The microspheres showed good flow properties (angle of repose 20°-28°), floating time of more than 12 h under stirring conditions and controlled drug release for more than 15 h[15].
- Naggar et al., 2001, developed sustained release system for ketoprofen designed to increase its residence time in the stomach. They prepared floating microparticles by the emulsion-solvent diffusion technique. Four different ratios of Eudragit S100 (ES) with Eudragit RL (ERL) were used to form the floating microparticles. The drug retained in the floating microparticles got decreased with increase in ERL content. All floating microparticles formulations showed good flow properties and packability. Scanning electron microscopy and particle size analysis revealed differences between the formulations as to their appearance and size distribution [16].

Types of floating multiparticulate drug delivery system

Floating multiparticulates drug delivery system can be divided into two systems:

1. Effervescent systems
2. Non-effervescent systems

1. Effervescent Systems

A. Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach[17].

B. Gas-generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme[18, 19]. These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the

stomach .Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.[20]

2. Non-Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibition 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.

a. Colloidalgel barrier systems

Hydrodymamically balance system (HBS) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms[20].

b. Microporous Compartment System

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.[21]

c. 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 a 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 fource over 12 h[21].

d. Hollow microspheres

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ehanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 h in vitro[21].

Methods of preparation of floating multiparticulate

Floating multiparticulates are prepared by solvent diffusion and evaporation methods to create the hollow inner core. 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. 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[10].

Characterization of floating multiparticulate

- **Micromeritic Studies of Floating Multiparticulates**

Floating multiparticulates are characterized by their micromeritic properties such as particle size, bulk and tapped density, compressibility index, true density and flow properties[22].

- **Particle size determination**

Size of multiparticulates affects the release rate of the drug. Increase in size, decreases the effective surface area which ultimately decreases the release rate. Size distribution analysis of microspheres was done by optical microscopy using motic microscope. A small quantity of microspheres was dispersed on the slide with the help of capillary tube. The diameters were sized using a suitable objective (10X and 40X). An average of 50 particles was calculated for each variable studied [23].

- **Bulk and Tapped density[24]**

Bulk and tapped densities were measured by using 10 ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated[24].

$$\text{Tapped Density} = \frac{\text{Mass of microspheres}}{\text{Volume of micropheres after tapping}}$$

- **Carr's Compressibility Index[24]**

Compressibility index (C.I.) or Carr's index value of microparticles was computed according to the following equation:

$$\%\ \text{Compressibility index (C.I.)} = \frac{(\rho t - \rho o)}{\rho t} \times 100$$

Where, ρt = tapped density, ρo = bulk density

The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

- **Hausner ratio[24]**

Hausner's ratio of microparticles was determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner's ratio} = \frac{\rho t}{\rho o}$$

Where, ρt = tapped density, ρo = bulk density

- **The Angle of repose (θ)**

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. Angle of repose of different formulations was measured according to fixed funnel standing method (*n*= 3)[25]. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper. The angle of repose was calculated by substituting the values of base radius 'r' and pile height 'h' in the following equation,

$$\tan \theta = \frac{h}{r}$$

Where, θ is the angle of repose, *h* is the height and *r* is the radius.

- **Scanning electron microscopy (SEM):**

Morphological examination of the surface and internal structure of the floating multiparticulate was performed by using a scanning electron microscope (SEM). For examination of the internal structure of the multiparticulates, they were cut in half with a steel blade[26].

- **X-ray diffraction technique (XRD) and differential scanning colorimetry (DSC):**

The determination of physical state of the drug in the multiple unit systems is important. There may be chances of change in crystallinity of the drug during the process, and such changes may influence the drug release properties. The crystallinity of drug can be studied by X-ray powder diffraction technique (XRD) and differential scanning colorimetry (DSC)[27].

- **Floating Behavior**

Fifty milligrams of the floating multiparticulates were placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant multiparticulate 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[28].

Buoyancy (%) = $W_f / W_f + W_s$

Where, W_f and W_s are the weights of the floating and settled microparticles

- ***In-Vitro* Release Studies**

In vitro drug release from the floating multiparticulates is complicated because the multiparticulates float and adhere to the inner surfaces of dissolution basket, which leads to the non-participation of multiparticulates or their surface in release study. Floating multiparticulates have the propensity to exhibit a buoyancy effect in vivo, but the development of a dissolution method as a quality control tool with the simulated buoyant condition is difficult.

The release rate of floating multiparticulate was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating multiparticulates equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml

samples were withdrawn at each 30 min interval, passed through a 0.25 μm membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate[21].

- ***In-Vivo* Studies**

The in vivo gastric retentivity of a floating dosage form is usually determined by g-scintigraphy [29] or roentgenography[30,31].

Mechanism of floating multiparticulates

The mechanism of multiparticulate formulation depends on the creation of an interfacial area, involving a polymeric material that forms an interfacial boundary and method of crosslinking to impart permanency. When multiparticulates 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 multiparticulates. However a minimal gastric content needed to allow proper achievement of buoyancy[15, 32].

Factors to be considered during formulation of floating multiparticulate[33]

- **Addition of polymer solution**

As reported that, the high surface tension of water caused the solidification and aggregation of polymer on the surface of aqueous phase. To minimize the contact of polymer solution with the air-water interface and to develop a continuous process for preparing microspheres, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the introduction of the polymer solution through the glass tube without contacting the surface of water. This method improved the yield of microspheres and reduced the extent of aggregate formation. As the polymer solution is continuously introduced into the main vessel, it will overflow from the top of the vessel together with the prepared microspheres, since most of the formed microspheres will float on the top of the aqueous phase. The microspheres, which overflow from the top of the vessel, can be collected in a container with an appropriate sieve size at the bottom.

- **Effect of rotation speed**

It is obvious that the rotation speed of propeller affects yield and size distribution of microspheres. As the rotation speed of propeller is increased, the average particle size decreases, while maintaining its morphology.

- **Effect of temperature**

The temperature of the dispersing medium is an important factor in the formation of microspheres as it controls the evaporation rate of the solvents. At lower temperature (10 ^{0}C), prepared microsphere has crushed and irregularly shaped morphology. The shell of the microsphere turnes translucent during the process, due to the slower diffusion rate of ethanol and dichloromethane. At higher temperatures (40 ^{0}C), the shell of the microsphere becomes thin and it might be due to faster diffusion of alcohol in the droplet into aqueous phase and evaporation of dichloromethane immediately after introducing it into the medium.

Advantages of floating multiparticulate drug delivery system[33]

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

Limitations of floating multiparticulate drug delivery systems[30]

1. The residence time in the stomach depends upon the digestive state. Hence, floating multiparticulate drug delivery systems should be administered after the meal.
2. The ability to float relies in the hydration state of the dosage form. In order to keep this microsphere floating i*n-vivo*, intermittent administration of water (a tumbler full, every 2 hours) is beneficial.
3. The ability of drug to remain in the stomach depends upon the subject being positioned upright.
4. Floating multiparticulate drug delivery systems are not suitable for the drugs that have solubility or stability problems in the gastric fluid.
5. Drug like Nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be a desirable candidate for floating multiparticulates drug delivery systems since the slow gastric emptying may lead to the reduced systemic bioavailability.

Applications of floating multiparticulate

1. Sustained Drug Delivery

Floating multiparticulates of non-steroidal anti inflammatory 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.

2. Solubility Enhancement

Floating multiparticulates 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.

3. 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.

4. Site-Specific Drug Delivery

Floating multiparticulates 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 sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.[21]

5. 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 bioavailabilities[34].

CONCLUSION

Though much research has been conducted to develop sustained release delivery systems, very few systems, which retained in the stomach for a long time, have been developed so far. Multiparticulate drug delivery systems provide several all the advantages including greater flexibility and adaptability of microparticulate dosage forms which gives clinicians and those engaged in product development powerful new tools to optimize therapy. These systems mainly consist of floating multiparticulate systems. Floating multiparticulate dosage unit is useful for drugs acting loatable in the proximal gastrointestinal tract. These systems are also useful for drugs, which are poorly soluble or unstable in intestinal fluids. The floating properties of these systems help in retaining these systems in the stomach for a long time. The floating multiparticulate drug delivery system 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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