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A Review on Floating Multiparticulate System For Gastric Retention

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ABSTRACT

Over the years, different formulation technologies for gastroretentive dosage delivery were investigated and patented. Well-designed controlled drug delivery system can overcome the problems of conventional therapy and enhance the therapeutic efficacy of a drug. There are various approaches in delivering a therapeutic substance to target site in a sustained controlled release fashion. One such approach is using multiparticulate as carriers for drugs. Such systems have advantages over single-unit dosage forms as they avoid the all-or-none gastric emptying nature of single-unit systems. However, multiparticulate dosage forms are gaining favor because of potential benefits like predictable gastric emptying, no risk of dose dumping, flexible release patterns and increased bioavailability with less inter- and intra-subject variability. 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- multiparticulate system, design and method of preparation, floating microspheres, beads, granules.

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INTRODUCTION

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment.[1] To develop a drug delivery system for oral administration, it is necessary to optimize not only the release rate of an active ingredient from the system but also the residence time of the system in the gastrointestinal tract.[2] Over the past 20 years several controlled delivery systems have been formulated.[3] Drug bioavailability of pharmaceutical oral dosage forms is influenced by various factors. One important factor is the gastric residence time (GRT) of these dosage forms. In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time.[4] Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach.[5,6] Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine.[7] Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid.[8]

Multiparticulate Systems

Floating drug delivery systems were first described by Davis in 1968.[9] While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system, after release of drug; the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. Most of the floating systems previously reported are single unit systems. A drawback of these systems is the high variability of the GI transit time due to their all-or-nothing emptying processes.[10, 11] However, bioavailability of the drug has been found to be reduced further with controlled release dosage forms, probably due to the fact that passage of the controlled release single unit dosage forms from absorption region of the drug is faster than its release.[12] In contrast, multiple unit dosage forms enjoy the advantage since they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release, thereby, reducing the intersubject variability in absorption and risk of local irritation.[3] Current technologies, such as oral multiparticulate drug-delivery systems (MDDS), have gained immensely in importance, not only because of their ability to control drug release, but also for the modified drug-release profiles they facilitate.[13] Lately, a wide variety of both natural and synthetic hydrophilic polyionic systems like alginates

have been investigated for preparation of multiple-unit floating dosage forms (FDFs).[14] The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above-mentioned disadvantages of single unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed.[15] Over the past three decades, advances in research aiming towards underlying principles to bring both commercial and therapeutic values to health care products, are contributing to novel drug delivery systems. These new and/or improved delivery systems work on various principles by providing variable/constant drug amounts over a particular time period in our body based on the fact that physiologic parameters display constancy over a time.[16] In recent pharmaceutical applications involving pulsatile delivery, multiparticulate dosage forms are gaining much favor over single-unit dosage forms**.**[17] There is clear evidence that multi-particulate systems can provide effective oral controlled release dosage forms**.**[18] These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.[10] Because of their smaller particle size these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability.[19] Indeed, the gastric emptying of a multiparticulate floating system would occur in a consistent manner with small individual variations. On each subsequent gastric emptying, sunk particles will spread out more uniformly over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way.[20, 21] Moreover, since each dose consists of many subunits, the risk of dose dumping is reduced.[22, 21] However, potential drug loading of a multiparticulate system is lower because of the proportionally higher need for excipients. [19]

Advantages and drawbacks of multiparticulate drug delivery systems

Advantages

Predictable, reproducible and short gastric residence time

Less inter- and intra-subject variability

Improve bioavailability

Reduced adverse effects and improved tolerability

Limited risk of local irritation

No risk of dose dumping

Flexibility in design

Ease of combining pellets with different compositions or release patterns.

Improve stability

Improve patient comfort and compliance

Achieve a unique release pattern

Extend patent protection, globalize product, and overcome competition

Drawbacks

Low drug loading

Proportionally higher need for excipients

Large number of process variables

Multiple formulation steps

Higher cost of production

Need of advanced technology

Trained/skilled personal needed for manufacturing

Purpose of Designing Multiparticulate Dosage Forms

The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit-to-unit variation.[20] For the optimum design of a CR oral dosage form, the key step is to understand the principles of GI dynamics such as gastric emptying, small intestinal transit, colonic transit, etc.[23] The concept of multiple-unit systems is characterized by the fact that the dose is administered as a number of subunits, each containing the active ingredient. The dose is then the sum of the individual subunits, and the functionality of the entire dose is directly correlated to the functionality of the individual subunits.[24] When multiple-unit systems are taken orally, the subunits of multiple-unit preparations distribute readily over a large surface area in the gastrointestinal tract and these small particles behave like liquids leaving the stomach within a short period of time. Their small size also enables them to be well distributed along the GI tract that could improve the bioavailability, which potentially could result in a reduction in local drug concentration, risk of toxicity, and side effects.[25] Inter and intra-individual variations in bioavailability caused by, for example food effects, are reduced.[26, 27] Multiple-unit systems are a common way of obtaining well-controlled regulation of the drug release rate from oral drug formulations, partly because they minimize the risk of dose dumping, and partly because the reproducibility in release profile is better than that of single-unit devices.[28] Because of their small particle size, multiparticulates can pass through the upper GI tract easily[29, 30] can reach the colon quickly and are retained longer in the ascending colon.[31] Therefore, a multiparticulate system of chitosan would be a desired dosage form for colon targeting.[32] The main advantage of multiple unit dosage forms is related to their in vivo behavior, e.g., increased uniformity of plasma levels and better reproducible bioavailability.[33] In

the multiple-unit system, the total drug is divided into many units. Failure of few units may not be as consequential as failure of a single-unit system. Other advantages of this divided dose include ease of adjustment of the strength of a dosage unit, administration of incompatible drugs in a single dosage unit by separating them in different multiparticulates and combination of multiparticulates with different drug-release rates to obtain the desired overall release profile. With regards to the final dosage form, multiparticulates can be filled into hard gelatin capsules or be compressed into tablets of which the former is more common. [34]

MECHANISM [35]

The mechanism of drug release from multiparticulates can be occur in the following ways:

Diffusion

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis

In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating

PREPARATION OF GASTRORETENTIVE MULTIPARTICULATE SYSTEM

Solvent evaporation method

The technique of microencapsulation by solvent evaporation s widely applied in pharmaceutical industries to obtain the controlled release of drug. The obtained polymer microspheres with drug trapped inside can degrade and release the encapsulated drug slowly with a specific release profile. This controlled drug release as outstanding clinical benefits: reducing of dosing frequency, ore convenience and acceptance for patients, and drug targeting to specific locations resulting in a higher efficiency**.** [36]

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.[37, 38, 39] After the formation of a stable emulsion, the organic solvent is evaporated

either by increasing the temperature under pressure or by continuous stirring. [40, 41] 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. 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. [42,39]

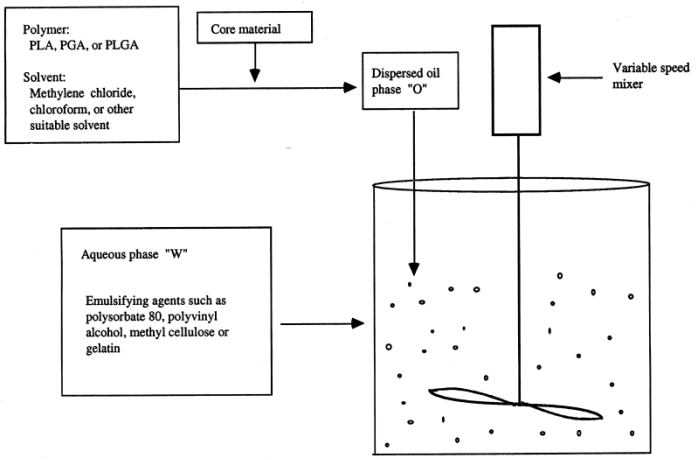

Figure. 1. Schematic diagram of O/W emulsion solvent evaporation method [37]

Ionotropic gelation method

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogels. Since, the use of alginates, gellan gum, chitosan, and carboxymethyl cellulose for the encapsulation of drug, ionotropic gelation technique has been widely used for this purpose. [43] The natural polyelectrolytes inspite, having a 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. Dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations produces the hydrogel beads. The cations diffuses into the drug-loaded polymeric drops, forming a three dimensional lattice of ionically crossed linked moiety. Biomolecules can also be loaded into these hydrogel beads under mild conditions to retain their three dimensional structure. [44, 45]

Researchers had developed floatable multiparticulate system with potential for intra gastric sustained drug delivery. Cross-linked beads are 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. [46]

Polyelectrolyte complexation technique

The quality of hydrogel beads prepared by ionotropic gelation method can also be further improved by polyelectrolyte complexation technique. The mechanical strength and permeability barrier of hydrogels can be improved by the addition of oppositely charged another polyelectrolyte to the ionotropically gelated hydrogel beads. For instance, addition of polycations allows a membrane of polyelectrolyte complex to form on the surface of alginate beads. [47, 48]

Large numbers of natural and chemically modified polyelectrolytes have been investigated and a schematic diagram of the preparation of hydrogel beads through ionotropic gelation and polyelectrolyte complexation is shown in below [44]

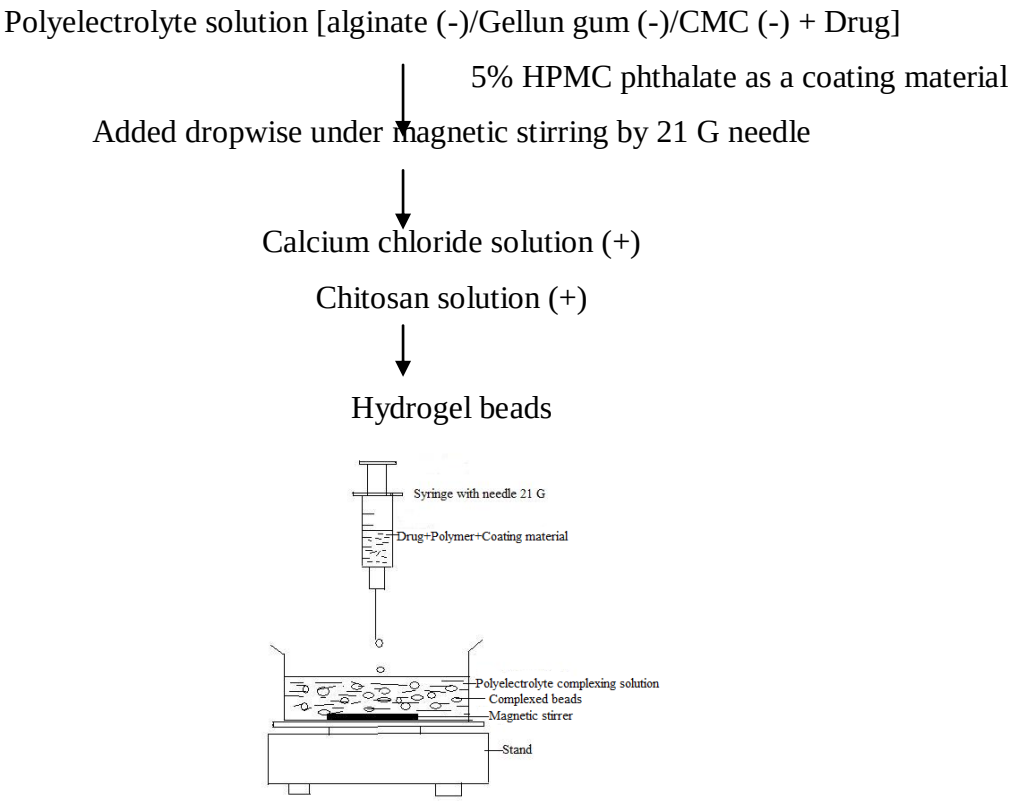

Figure. 2. Schematic diagram of the preparation of hydrogel beads by ionotropic gelation and polyelectrolyte complexation.

Emulsion solvent diffusion method

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuse gradually out of the emulsion

droplets in to the surrounding aqueous phase and the aqueous phase diffuse in to the droplets by which drug crystallizes. [15]

Kawashima and colleagues 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**.** [49]

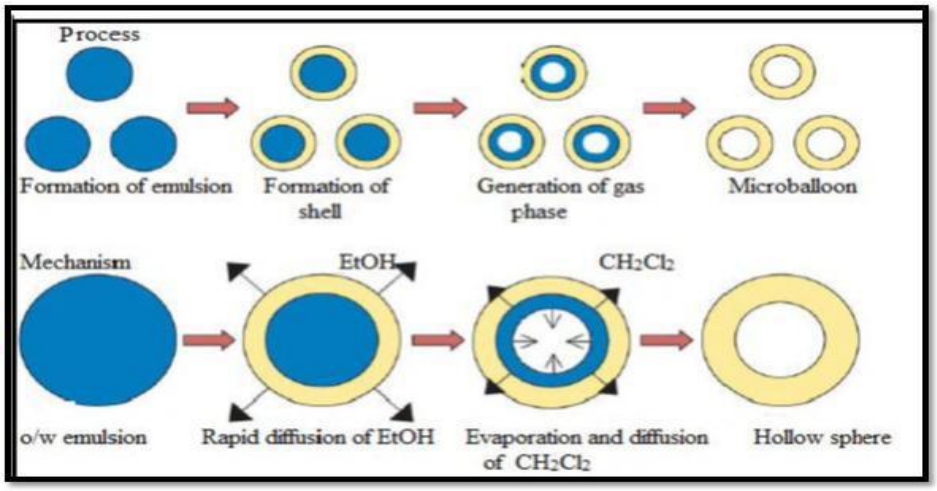

Figure. 3. Preparation technique (emulsion-solvent diffusion method) and mechanism of 'microballoon' formation.

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. [50, 51]

Novel method for foam powder

Furthermore, a novel multi-particulate gastroretentive drug delivery system based on low-density foam powder has been proposed and its performance demonstrated invitro**.**[52] 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 4a). 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 invitro. 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 4b). [53] 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. [54]

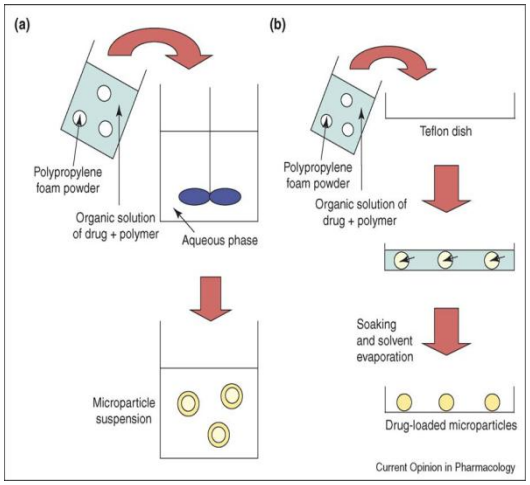

Figure 4 Schematic presentation of the preparation of floating microparticles based on low-density foam powder, using (a) the solvent evaporation method or (b) the soaking method. Reprinted from Streubel A: Oral delivery systems with modified drug release.

TYPES OF GASTRORETENTIVE MULTIPARTICULATE DRUG DELIVERY SYSTEM

Floating beads

This porous multiple unit system is based on the swelling capacity and gel-barrier formation of alginate salts and their suitability both for gastro-retentive and modified release systems. Alginate beads are prepared by freeze-drying process. Sodium alginate solution is dropped into

calcium chloride aqueous solution, leading in precipitation and formation of calcium alginate beads. These beads are then separated and immersed into liquid nitrogen and freeze dried at -40°C. Alginate beads may be retained in the stomach up to 12 hours and may release the active compound by diffusion and/or erosion.[55,56] The spherical beads in the size range of 1-2.5 mm in diameter can be prepared by dropping the aqueous solution containing polymer and drug in to an aqueous solution of calcium chloride, causing precipitation of polymer in presence of calcium ions. The beads are then separated and dried for suitable time to attain constant weight.[15] The floating beads can be made by solvent evaporation technique, or by incorporating of gas forming agent such Calcium carbonate or porous structural element.[57, 58,59]

Floating alginate beads are particularly effective for site specific-controlled release of antibacterial agents effective against harmful stomach bacteria suchas H. pylori. [60, 61]

Calcium-induced alginate gel beads (Alg-Ca) have been developed in recent years as a unique vehicle for drug delivery. Alg-Ca is rapidly formed by gelation of alginic acid in the presence of calcium ions and is able to incorporate some compounds such as drugs or polysaccharides in the gel matrix. [62, 63] The beads have been used in various ways in the gastrointestinal tract, for example, for sustained release of drugs or to adsorb bile acid. [64] Other studies have been made of gastroretention in attempts to improve control over drug release or to achieve a site-specific delivery. [65, 66, 67] The role of mucoadhesives and floating properties of the alginate gel forms as well as the effect of varying dosage have been investigated. The floating system has been found to be particularly promising for drug gastroretention.[68, 69] For example, lyophilized calcium alginate prolonged gastroretention in human volunteers.[70, 71] When alginate gel beads containing chitosan were administrated orally to guinea pigs, the beads floated on the gastric juice and released the drug in the stomach. This method has been widely employed to prevent recurrence of peptic ulcer disease, a phenomenon that is correlated to infection by Helicobacter pylori.[72, 73]

Recently, much research efforts have been concentrated to develop calcium alginate beads loaded with various low molecular weight therapeutic agents. In various studies, alginate beads have been used as excellent vehicles. Rabbit articular chondrocytes immobilized in alginate beads maintained normal morphology and metabolic activity for more than two weeks using calcium, barium, and strontium as gel forming agents. [74] Another important property of alginate beads is their re-swelling ability.

Floating microspheres

Hollow microspheres are spherical empty particles without core. These microspheres are made from different kind of hydrocolloids (polymers, gel forming agents, polysacharides). Gastro-

retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents, remain in stomach for prolonged period and release the active compound in controlled manner. 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, entraps gas (enables floating) and stimulates consequent drug release (diffusion, erosion). Hollow microspheres are prepared by solvent diffusion and evaporation methods**.** [55, 56]

Kawashima and other researchers developed hollow microspheres (microballoons, MB) in order to prolong GRT of the dosage form. This gastrointestinal transit-controlled preparation is designed to float on gastric juice with a specific density of less than 1.[75, 76] The shape and surface morphology of the microspheres were characterized by optical and scanning electron microscopy. The microspheres exhibit prolonged drug release (8 h) and remained buoyant for more than 10 h. In vitro studies demonstrated diffusion-controlled drug releases from the microspheres.[55] Polymeric microspheres have attracted considerable attention, as drug carriers for controlled release systems.[77] Particulate carriers are ideal in providing a constant therapeutic and non-toxic level of the drug. Various proteins, polysaccharide and other polymeric materials have been investigated as drug carriers, and many techniques have been pointed out to synthesise nanoparticles, microparticles and beads.[78, 79] Pivotal studies in Nottingham University, UK, have revealed that oral dose forms containing finely divided ion exchange resins can provide prolonged gastric residence and uniform distribution within the stomach. [80] For such an effect, the particles will need to be small from a mechanical consideration and of low density so that they might be able to float. A positive charge should also confer an advantage. Adherence to the wall of the stomach will be possible during the emptying process in both the fed and fasted state, assuming that the Mucoadhesive properties of the particles have not been modified by the stomach contents, in particular, non-adherent mucus (Figure 5). [81]

Proposed mechanism for retention of bioadhesive microspheres in the human stomach. A capsule containing the bioadhesive microspheres is administered with water and the released microspheres float on the fluid in the stomach. During the process of gastric empyting, a proportion of the bioadhesive microspheres adheres to the stomach wall to provide gastroretention.

Floating granules

Multi unit dosage from such as granules or pellets may be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping. [82]

Floating granules can be prepared using a drug with suitable lipophilic polymer having low density. The polymers used for these granules are usually meltable at moderate temperature allowing the use of solvent free melt granulation technology for granulation.[15] Pellets are manufactured by both wet and dry granulation techniques or by layering. Extrusion–spheronization is a wet-granulation technique that helps in the preparation of pellets or spherical agglomerates. The process involves a blending stage, in which active ingredients are blended with excipients and mixed with suitable binding solutions to form a heavy plastic mass. This mass is subjected to extrusion to form extrudates of equal length. After extrusion, the materials undergo a spheronizing stage that rounds extrudates by cutting them and rolling them into spheres.[13] The most important application of extrusion in the pharmaceutical industry is in the preparation of granules or pellets of uniform size, shape, and density, containing one or more drugs.[83] The process involves a preliminary stage in which conventional blenders, followed by addition of liquid phase and further mixing to ensure homogeneous distribution, mix dry powders, drug, and excipients.[84] The wet powder mass is extruded through cylindrical dies or perforated screens with circular holes of typically 0.5–2.0 mm diameter, to form cylindrical extrudates.[85] Melt extrusion for the manufacture of pellets had revealed the potential for controlled release of polymer embedded drugs and limitations.[86]

CHARACTERIZATION OF GASTRORETENTIVE MULTIPARTICULATE SYSTEM

Micromeritics properties [87, 88]

The multiparticulates are characterized by their micromeritic properties, such as true density, tapped density, compressibility index and flow properties.

The tapping method was used to determine the tapped density and percent compressibility index as follows:

Tapped density= Mass of microspheres/ Volume of microspheres after tapping [89]

Hausner ratio, and Carr index (% compressibility index) were determined to predict flowability. A higher Hausner ratio indicates greater cohesion between particles, while a high Carr index is indicative of the tendency to form bridges. Hausner ration and Carr index were calculated using the formula. [90]

$$\% \text{ Compressibility index} = [1 - V/Vo]*100$$

Here V and Vo are the volumes of the sample after and before the standard tapping, respectively.

True density was determined using a benzene displacement method. The microspheres were immersed in 0.02% tween 80 solutions for three days in a metal mesh basket. The submerged

microspheres were used for density measurements. True density of floating microspheres was determined by liquid displacement method using relative density bottle.[2]

Porosity (ε) was calculated using the equation:

$$\varepsilon = [1 - Pp/Pt]*100$$

where Pt and Pp are the true density and tapped density, respectively.[91]

Angle of reposeθ of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method and calculated as

$$\text{Tan } \theta = 2H/D$$

where 2H/D is the surface area of the free standing height of the microspheres heap that is formed on a graph paper after making the microspheres flow from the glass funnel. [92]

Particle size and shape [93]

The size was measured using an optical microscope, and the mean particle size was calculated by measuring 200–300 particles with the help of a calibrated ocular micrometer. SEM provides higher resolution in contrast to the LM. [94] 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 [95] 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.

Floating time and dissolution:

The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 37°C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole.lit-1 HCl as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.[96]

In vitro floating ability study

The floating abilities of the effervescent-layered pellets and the coated effervescent-layered

pellets (complete multiple-unit FDDS) were determined using USP paddle apparatus (50 rpm, 37±0.2°C, 900 ml, 0.1N HCl). Twenty pellets were placed in the medium; the time to float and duration of floating (floating time) were measured by visual observation. The percentage of floating pellets was calculated by the following equation: [97, 98, 99]

$$\text{Floating pellets (\%)} = \frac{\text{number of floating pellets at the measure time}}{\text{Initial number of the pellets x 100}}$$

Production Yield [100]

Production yield depends on the ratio of polymer and effervescent agent can be calculated by the following formula:

Production Yield = Practical Yield (Microcarriers)/ Theoretical Yield (Polymer + Drug)X 100

Drug loading and entrapment efficiency [101]

The drug loading (DL) and encapsulation efficiency (EE) was calculated according to the following equation:

$$DL\ (\%) = WD/WT*100$$

DL: drug loading; WD: the weight of the drug loaded in the microspheres; WT: the total weight of the microspheres.

$$EE\ (\%) = WA/WT*100$$

EE: encapsulation efficiency; WA: actual drug content; WT: theoretical drug content.

Swelling studies

Swelling studies of the beads were carried out in triplicate by gravimetric method. [102] Known weight of the beads were taken and immersed in excess of distilled water for definite time interval at 37 ◦C and then beads were remove and weighed immediately. The difference in weight gave the amount of water uptake by the beads after definite time intervals (30 min). Effect of pH of the swelling medium on swelling kinetics was also studied. The percentage swelling (*P*s) of the beads was calculated as: [103]

$$Ps = [Ws - Wd]/\ Wd\ x\ 100$$

Where *W*s is the weight of swollen beads and *W*d is the weight of dried beads.

In vitro release study

This was performed for each sample of beads. The paddles were rotated at 50 rpm, the volume of the media used was 900 ml and the temperature was maintained at 37 °C±1°C. The studies used media of different pH in an attempt to simulate the various pH values found throughout the GIT. [104] Five ml sample was withdrawn at each 30 min interval, passed through a 5 μm membrane

filter (Millipore), and analyzed spectrophotometrically to determine the concentration of drug 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.

Gamma-Scintigraphy

X-ray/gamma scintigraphy is currently a very popular method for evaluating parameters for floating dosage forms. [105] It helps to locate the dosage form in the GIT and it can be used to predict and correlate the gastric emptying time and the passage of the dosage form in the GIT. Here, the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner.[106] In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract. [107, 108]

Gamma -Emitting radioisotopes compounded into CR-DFs has become the state-of-art for evaluation of gastroretentive formulation in healthy volunteers. A small amount of a stable isotope e.g. Sm, is compounded into DF during its preparation. The main drawbacks of gamma - scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, lo resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceuticals. [109, 110]

Drug-excipient (DE) interactions:

This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicate the DE interaction. [6]

CONCLUSION

Gastro retentive multiparticulate have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. Multiparticulate dosage forms are gaining much favor over single-unit dosage forms as these 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. The potential benefits include increased bioavailability; predictable, reproducible and generally short gastric residence time, no risk of dose dumping; reduced risk of local irritation, and the flexibility to blend pellets with different compositions or release patterns. Continuous input of the drug following Controlled Release Gastro Retentive Dosage Form administration produces blood drug concentrations within a narrower range compared to the immediate release dosage

forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index. 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 narrow 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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