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Microspheres: An Overview and Current Technological Development of Floating Drug Delivery System

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ABSTRACT

There are various departments of medicine like cancer, pulmonary, cardiology, radiology and gynaecology etc, numerous drugs are used and they are delivered by various types of drug delivery system. Among them microspheric drug delivery system has gained enormous attention due to its wide range of application as it covers targeting the drug to particular site to imaging and helping the diagnostic features. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems, swelling and expanding systems, bioadhesive systems and high-density systems. The purpose of the review is to compile various types of microspheres, different methods of preparation, the current technological developments of FDDS, their applications and also various parameters to evaluate their efficiency.

Keywords: Microspheres, Floating Drug Delivery System, Gastric residence time.

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INTRODUCTION

The main goal of any drug delivery system is to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. The pointing of the goal is towards the two main aspects regarding drug delivery, namely spatial placement and temporal delivery of a drug. Spatial placement means targeting a drug to a specific organ or a tissue while temporal delivery refers to controlling the rate of drug delivery to that specific organ or a tissue.[1] Frequent administration of drug is necessary when those have shorter half life and all these leads to decrease in patient's compliance.[7]In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect , adverse effect decreases by lowering peak plasma concentration.[2] The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time.

One such in Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system.[2] Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level.[4] It has a particle size of (1-1000nm).[3] Further, currently available slow release oral dosage forms, such as enteric coated/ double-layer tablets which release the drug for 12-24 hours still result in inefficient systemic delivery of the drug and potential gastrointestinal irritation. Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided.4 Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.[5] 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 Gastroretentive floating microspheres.[6]

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. 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. Bio/mucoadhesive systems 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 first described by Davis (1968), are low-density systems 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. 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.[6]

METHOD OF PREPARATION OF MULTIPARTICULATE (MICROSPHERES) SYSTEM [8]

Emulsion technique

i. Single emulsion technique
ii. Double emulsion technique

Polymerization

i. Normal polymerization
ii. Interfacial polymerization

Phase separation Coacervation Technique

Spray Drying and spray congealing

Solvent extraction (evaporation)

i) Oil-in-Water Emulsion Solvent evaporation technique.
ii) Oil-in-Oil (Non-Aqueous) Emulsion Solvent evaporation technique

Ionotropic Gelation Method [9]

Emulsion technique

Single Emulsion Technique

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil with the help of cross linking agent.

Double Emulsion Technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion such as w/o/w. This method can be used with both natural as well as synthetic**.**

Polymerization Technique

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

Normal Polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. Bulk polymerization has an advantage of formation of pure polymers.

Interfacial Polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed.

Phase Separation Coacervation Technique

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer.

Spray Drying and Spray Congealing

These methods are based on the drying of the mist of the polymer and drug in the air. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 µm. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively.

Solvent extraction (evaporation)[9]

This technique is widely employed by large number of pharmaceutical industries to obtain the controlled release of drug. This approach involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is

reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilisation . For emulsion solvent evaporation, there are basically two systems which include oil-inwater (o/w) and water-in-oil (w/o) type.

Oil-in-Water Emulsion Solvent evaporation technique [9]

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

Oil-in-Oil (Non-Aqueous) Emulsion Solvent evaporation technique [9]

This oil-in-oil (sometimes referred as water-in-oil) emulsification process is also known as non aqueous emulsification solvent evaporation. In this technique, drug and polymers are codissolved at room temperature into polar solvents such as ethanol, dichloromethane, acetonitrile etc. with vigorous agitation to form uniform drug–polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at 500 revolutions per minute (rpm) and room temperature over a period of 2–3 hrs to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the microparticles are separated by filtration through a Whatmann filter paper, washed thrice with n-hexane, air dried for 24 hrs and subsequently stored in dessicator. Span 60 is generally used which is non ionic surfactant. Span 60 has an HLB value of 4.3 and acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium.

Ionotropic Gelation Method [9]

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

loaded polymeric solution using syringe into the aqueous solution of polyvalent cations as depicted in Fig.16. The cations diffuses into the drug loaded polymeric drops, forming a three dimensional lattice of ionically cross linked moiety. Microspheres formed left into the original solution for sufficient time period for internal gelification and they are separated by filtration. Natural polymers such as alginates can be used to improve drug entrapment and are widely used in the development of floating microspheres.

Mechanism of Drug Release

Theoretically, the release of drugs from biodegradable microspheres can be classified broadly into four different categories. But in actual practice, the mechanism is more complex and an interplay of different mechanisms may operate.[10] Degradation controlled monolithic system In degradation controlled monolithic microsphere systems, the drug is dissolved in the matrix and is distributed uniformly throughout.

The drug is strongly to the matrix and is released only on degradation of the matrix. The diffusion of the drug is slow compared with the degradation of the matrix. When degradation is by homogeneous bulk mechanism, drug release is slow initially and increases rapidly when rapid bulk degradation starts. Drug release from such type of devices is independent of the geometry of the device. Release from a sphere is governed by the equation, where Mt is the amount of the agent released at time t, M∞ is the amount at time t∞ is the time for total erosion.

Mt /M∞ = 1-[(1-t/ t∞)[10]

Diffusion controlled monolithic system

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Degeneration of the polymer matrix affects the rate of release and has to be taken into account. Rate of release also depends on whether the polymer degrades by homogeneous or heterogeneous mechanism. Diffusion controlled reservoir systems here the active agent is encapsulated by a rare controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix. Polymer that remains as such till the complete, release of drug and then degrades by homogenous mechanism so that the device is removed from the body is better for this type of delivery. Erodible poly-agent system In this case the active agent is chemically attached to the matrix and the rate of biodegradation of the matrix is slow compared to the rate of hydrolysis of drug polymer bond. Assuming that the rate of diffusion of the active agent from the matrix to the surrounding is rapid, the limiting step is the rate of cleavage of the bond attaching drug to the polymer matrix.[11]

List of Polymers Used In Floating Multiparticulate (Microspheres) System

Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Ethyl cellulose, Agar, Polyethylene oxide, Acrylic resins; etc.

Classification Of Floating Drug System [14,15]

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy.

Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrixforming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene .The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

Hydrodynamically Balanced Systems [14,15]

These are single-unit dosage forms, containing one or more gelforming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most common used excipient, although Hydroxyethylcellulose (HEC), Hydroxy-propylcellulose (HPC), Sodium Carboxy methylcellulose (NaCMC), agar, carrageenans or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Fig. 1)

Hollow microspheres / Microballoons [15]

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 400C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hrs.

Alginate beads [13]

Multi-unit floating dosage forms have been developed from freezedried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and

freeze-dried at -400C for 24 hrs, leading to the formation of a porous system, which can maintain a floating force for over 12 hrs. These floating beads gave a prolonged residence time of more than 5.5 hrs.

Effervescent Floating Dosage Forms

Gas Generating Systems [14,15]

These are matrix type of systems prepared with the help of swellable polymers such as Methyl cellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provide buoyancy to the dosage forms. In single unit systems, such as capsules or tablets effervescent substances are incorporated in the hydrophilic polymer and CO2 bubbles are trapped in the swollen matrix (Fig.2a). In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 hrs. In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 hrs. Bilayer or multilayer systems have also been designed. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers (Fig. 2b). Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO2 (Fig. 2c).

Semipermeable membrane[15]

The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer. As mentioned previously, multiple unit systems avoid the ‘‘all or nothing’’ emptying Process. However, it is essential that the units remain dispersed and suspended individually in the gastric fluid and not agglomerate into a mass floating at the top of the stomach . In the beginning of the 1990s, Ichikawa et al. reported a double layered coated system in the form of granules. It comprised an inner effervescent layer (bicarbonate and tartaric acid) and an outerswellable membrane (polyvinyl acetate and shellac). The system floated completely within 10 min and 80 % remained floating over a period of 5 hrs. In vivo studies have been carried out in beagle dogs and humans in the fed state using granules loaded with barium sulphate as a radio opaque marker. Most floated in the stomach within 10 min and remained so for at least 3 hrs as observed by Xray photography (Fig. 3)

Low-density systems [14,15]

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘‘microballoons’’ because of the low-density core (Fig. 4a). Streubel et al. developed foam-based floating microparticles consisting of propylene foam powder, drug (chlorpheniramine maleate, diltiazem HCl, theophylline or verapamil HCl) and polymer n (Eudragit RS\ or polymethyl methacrylate). They were

prepared by soaking the microporous foam carrier with an organic solution of drug and polymer, and subsequent drying. The mixture was poured into an organic liquid (ethanol or methylene chloride) forming a suspension. The polypropylene foam particles acted like microsponges, absorbing the organic liquid, and becoming freeflowing, low-density microparticles following solvent evaporation (Fig.4b). Good in vitro buoyancy was observed in most cases and a broad variety of drug release patterns could be achieved by varying drug loading and type of polymer: more than 77% or 98% of particles floated for at least 8 hr depending on the polymer type (Eudragit RS or polymethyl methacrylate, respectively) and initial drug loading of the system (10% or 23%).Based on a similar approach, the same group developed a single unit, floating system, consisting of low-density polypropylene foam powder, matrix-forming polymers (HPMC, polyacrylates, sodium alginate, corn starch, carrageenan, agar, guar gum, and Arabic gum), drug and filler (Fig. 4). All the tablets remained floating for at least 8 hrs in 0.1N HCl at 37 0C. The release rate could effectively be modified by varying the matrix-forming polymer/foam powder ratio, the initial drug loading, the tablet geometry (radius and height), the type of matrixforming polymer, the use of polymer blends and the addition of water soluble or insoluble fillers (such as lactose or microcrystallalinecellulose)

Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles (Fig.5) on contact with gastric fluid. Formulations also typically contain antiacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with Liquid Gaviscon\ (GSk).

Expandable systems [15]

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required: a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release. Unfoldable and swellable systems have been investigated. Unfoldable systems are made of biodegradable polymers. The concept is to make a carrier, such as a capsule, Incorporating a compressed system which extends in the stomach. Caldwell et al. proposed different geometric forms (tetrahedron, ring or planar membrane [4-lobed, disc or 4-limbed cross form]) of bioerodible polymer compressed within a capsule (Fig.6).

Curatolo and Lo designed a kind of spring system, where the arms are fixed on the system by a gelatin band. The gelatin dissolves in the stomach, releasing the mechanically preferred extended form (Fig. 7a). Sonobe et al. developed a ‘‘Y’’ form system, with shape, size and durability enabling retention in the stomach.

The centre of the system is made of shape memory material, the three arms of the ‘‘Y’’ are erodible material which serves as a drug reservoir and whose rate of degradation

controls the gastric retention time. A third component provides the link between the arms and the centre (Fig. 7b). Klausner et al. described a levodopa gastroretentive dosage form, based on unfolding polymeric membranes, that combines extended dimensions (5 cm×2.5 cm) with high rigidity (Fig. 7c). It is folded into a large gelatin capsule (size 00 or 000). In vitro studies showed that the drug delivery system reached its unfolded form in 15 min. This was confirmed in vivo in beagle dogs and the extended form was maintained for at least 2 hrs. In humans, 67% of drug delivery systems containing levodopa were retained in the stomach during 5 hrs. The plasma concentration time curve was very similar to that of the reference drug (Sinemet CRc), but showed an extended absorption phase. Rigidity of the system was a crucial parameter. Thus, a system with an extended size but with a lack of high rigidity was not retained in the stomach. Swellable systems are also retained because of their mechanical properties. The swelling is usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids. The bulk enables gastric retention and maintains the stomach in a ‘‘fed’’ state, suppressing housekeeper waves. In 1980s, Mamajek and Moyer patented a drug reservoir, surrounded by a swellable expanding agent.

The whole system was coated by an elastic outer polymeric membrane (Fig. 8a), which was permeable to both the drug and body fluids and could control drug release. The device gradually decreased in volume and rigidity as a result of depletion of drug and expanding agent and/or bioerosion of the polymer envelope, enabling its elimination. Urquhart and Theeuwes developed a system containing tiny pills, with a very high swelling ratio enabling up to 50-fold volume increase. They were coated by wax to control drug release and dispersed in a matrix of polymeric hydrogel (Fig. 8b). In body fluids, the system swelled and the tiny pills released the drug in the stomach. The reservoir could leave the stomach following hydrolysis and bioerosion.

Bioadhesive or Mucoadhesive Systems [13]

These systems permit a given drug delivery system (DDS) to be incorporated with bio/mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying. However, the mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence. The stomach is a size-filtering system and so it would seem ideally suited to retaining a DDS that is larger than the pylorus. The drawback is that the DDS is not small enough to be taken orally if sizes larger than the pylorus are required. Several systems have been investigated to encourage gastric retention using increasing size of DDS. Systems have been based on expansion due to gases and swelling due to intake of external liquids(Fig.9).

Magnetic systems [15]

This system is based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Ito et al. used this technique in rabbits with bioadhesives granules containing ultrafine ferrite (g-Fe2O3). They guided them to the oesophagus with an external magnet (¨1700 G) for the initial 2 min and almost all the granules were retained in the region after2 hrs. Although

these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance(Fig.10).

DEVELOPMENT OF FLOATING MULTIPARTICULATE (MICROSPHERES) SYSTEM [12]

Multiparticulate drug delivery system applies specially to multiple particles such as pellets, beads, microspheres, microcapsules. Considerable research efforts have been spent on oral sustained or controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage forms. 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(Fig.11).

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.

Mechanism of Floating Multiparticulate (Microspheres) System [16]

The multiparticulates float on the stomach contents, and then adhere to the mucous linings as the stomach empties (Fig.12). The release of drug from the system can be controlled to coincide with the half-life emptying of the system from the 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.

Characterization of Multiparticulate (Microspheres) System [17]

Floating microspheres are characterized by their Micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties.

Particle size determination [18]

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.

Bulk and Tapped density [18]

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

Tapped Density = Mass of microsphere / Volume of microsphere after tapping

The compressibility index was calculated using following formula:

Compressibility Index = Tapped Density – Bulk Density / Tapped Density × 100

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

Floating Behavior [18]

50 milligrams of the floating microspheres 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 hrs, the layer of buoyant microspheres was pipette 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 (%) = Weight of floating microsphere / Initial weight of floating microsphere x100

***In-Vitro* Release Studies [18]**

The release rate of floating microspheres was determined in a United States Pharmacopoeia USP XXIII basket type dissolution apparatus. A weighed amount of floating microspheres 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 millilitres 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°C 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.

DEE (Drug Entrapment Efficiency)

Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at a

specific wavelength against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula:

DEE = (Amount of drug actually present /Theoretical drug load expected) × 100

IR Spectra

FTIR spectra of pure drug, polymer , 1:1 and 2:1 microspheres were obtained in KBr pellets at moderate scanning speed between 4000-200cm-1in a Perkin- Elmer FTIR Spectroscope.

Yield of Microspheres

The prepared microspheres with a size range of 251-µm were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (Actual weight of product / Total weight of excipient and drug) × 100

Scanning electron microscopy (SEM)

Morphological examination of the surface and internal structure of the dried beads was performed by using a scanning electron microscope (SEM). For examination of the internal structure of the beads, they were cut in half with a steel blade.

X-ray diffraction

Change in crystalinity of drug can be determined by this technique. Microperticles and its individual components were analysed by the help of D & discover (Bruker, Germony). Scanning range angle between 8 ^{0}C - 70 ^{0}C.
Scan speed - 4^{o}/min
Scintillation detector
Primary silt=1mm
Secondary silt=0.6 mm.[17]

Thermal analysis

Thermal analysis of microcapsule and its component can be done by using- Differential scanning calorimetry (DSC) Thermo gravimetric analysis (TGA) Differential thermometric analysis (DTA). Accurately the sample was weighed and heated on alumina pan at constant rate of 10oc/min under nitrogen flow of 40 ml/min.[17]

UV-FTTR (Fourier transform infra red)

The drug polymer interaction and also degredation of drug while processing for microencapsulation can be determined by FTIR.[20]

Stability studies

By placing the microspheres in screw capped glass container and stored them at following conditions:

1. Ambient humid condition
2. Room temperature (27+/-2 0C)
3. Oven temperature (40+/-2 0C)
4. Refrigerator (5 0C -80C).

It was carried out of a 60 days and the drug content of the microsphere was analysed.[19]

Zeta potential

The polyelectrolyte shell was prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles were determined by zeta potential measurement.[21]

Application of Floating Microparticulate Drug Delivery System [16]

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.

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.

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.

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.

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.

Table 1: List of drugs explored for various floating dosage forms

Dosage Form	Drugs/References
Microspheres	Aspirin, griseofulvin, p-nitroaniline[32] Ibuprofen[33] Terfenadine[34] Tranilast[31,33]
Granules	Diclofenac Sodium[35] Indomethacin[36] Prednisolone[37]
Films	Cinnarizine[38] Drug Delivery Devices[34]
Powders	Several basic drugs[40]
Capsules	Chlordizepoxide HCl[41] Diazepam[29,41,42] Furosemide[43] L-Dopa and benserazide[44] Misoprostol[30,45] Propranolol HCl[46] Ursodeoxycholic acid[47]
Tablets/Pills	Acetaminophen[48,49] Acetylsalicylic acid[50] Amoxycillin trihydrate[51] Ampicillin[52] Atenolol[53,54] Chlorpheniramine maleate[24] Cinnarizine[38] Diltiazem[55] Fluorouracil[56] Isosorbide mononitrate[57] Isosorbide dinitrate[58] p-Aminobenzoic acid[58,59] Piretanide[54] Prednisolone[60] Quinidine gluconate[27] Riboflavin-5' –phosphate[24,61] Sotalol[62] Theophylline[22,23,63] Verapamil HCl[64-66]

[a] Numbers in parentheses indicate the references.

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Table 2: Effects of food on GRTs of floating and non-floating (control) dosage forms

a Values are represented as mean (h); *n*5number of healthy human volunteers.

Drug	Dosage Form	GRT (h)		References
		NFDS	FDDS	
Diazepam	Capsules	1.0-1.5	4.0-10.0	[29,41,42]
Ethmozine (Moricizine HCl)	Tablets	1-1.5	>6	[67]
Gentamycine Sulfate	Tablets	1-2	>4	[68]
Isradipine	Capsules	0.15-2.87[b]	2.4-4.8[b]	[26]
Metoprolol Tartarate	Tablets	1-1.5	5-6	[69]
Miocamycine	Tablets	3-4	>7	[70]
Pepstatin	Minicapsules	NR	3-5[b]	[71]
Salbutamol Sulfate	Capsules	NR	8-9	[72]
Tranilast	Microballoons	NR	>3	[31]

b Results are expressed as gastric emptying times (GET).
c Floating capsules.

Table 3: Comparison of GRTs of floating and non-floating solid dosage forms[a]

Dosage forms [References]	Non-floating		Floating	
	Fasted	Fed	Fasted	Fed
Isradipine caps[26]	1.59 (*n*=5)	2.15 (*n*=4)	1.0 (*n*=5)	3.60(*n*=4)
Radiolabeled tabs [b][25]	1.65 (*n*=4)	4.43 (*n*=4)	0.82 (*n*=4) 3.37 (*n*=8) [c]	5.25 (*n*=4) 7.0 (*n*=8) [c]
Radiolabeled tabs [b][27]	1.1 (*n*=7)	1.32 (*n*=7)	1.1 (*n*=7)	7.15 (*n*=7)
Radiolabeled tabs[28]	2.53 (*n*=4)	6.27 (*n*=4)	2.2 (*n*=4)	6.77 (*n*=4)
Theophylline[23]	2.32 (*n*=3)	7.54 (*n*=3)	1.57 (*n*=3)	7.15 (*n*=3)

[a] GRT , gastric resident time ; NFDS , non-floating delivery system ; FDDS , floating drug delivery system .
[b] value obtained in fed state ; NR , not reported.

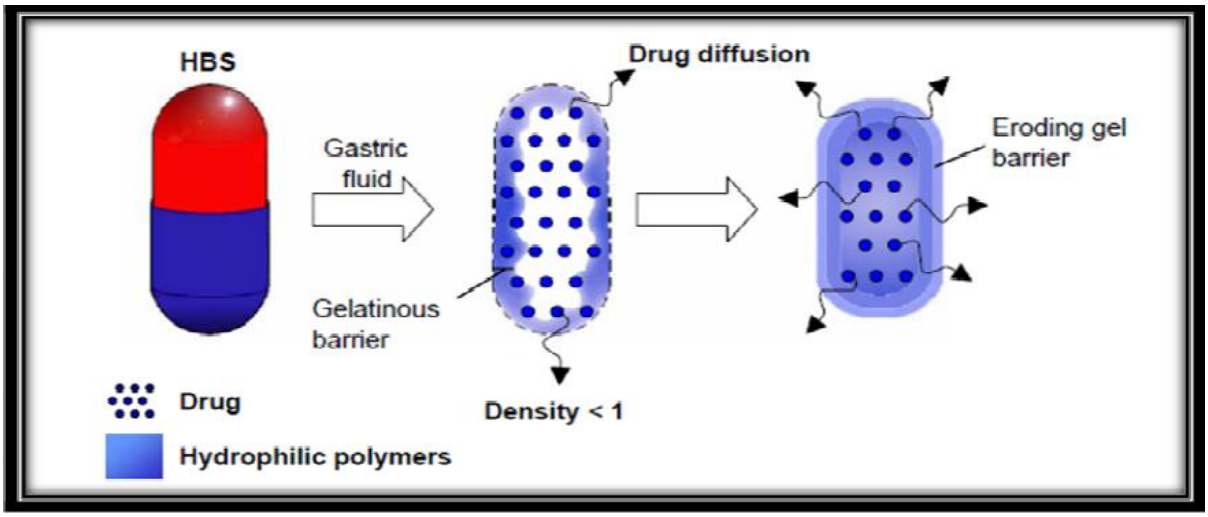

Fig. 1: Hydrodynamically balanced system (HBS). The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier. Based on Hwang et al. And Dubernet. Used with permissions.[14,15]

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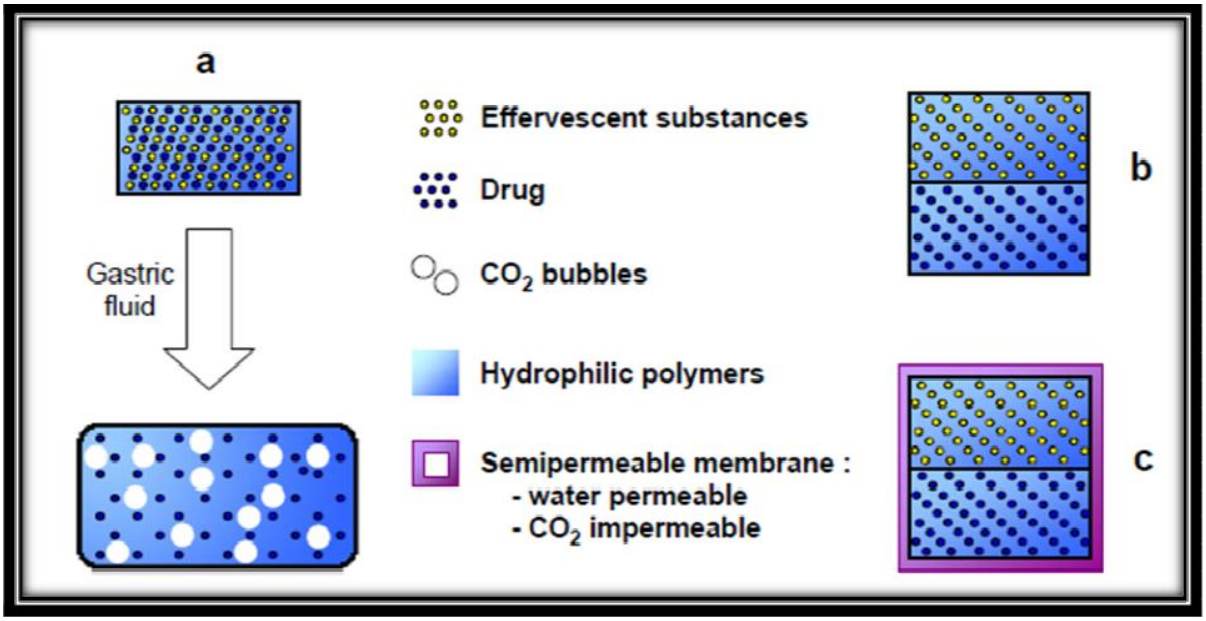

Fig. 2: Gas-generating systems. Schematic monolayer drug delivery system (a). Bilayer gas-generating systems, with (c) or without (b)

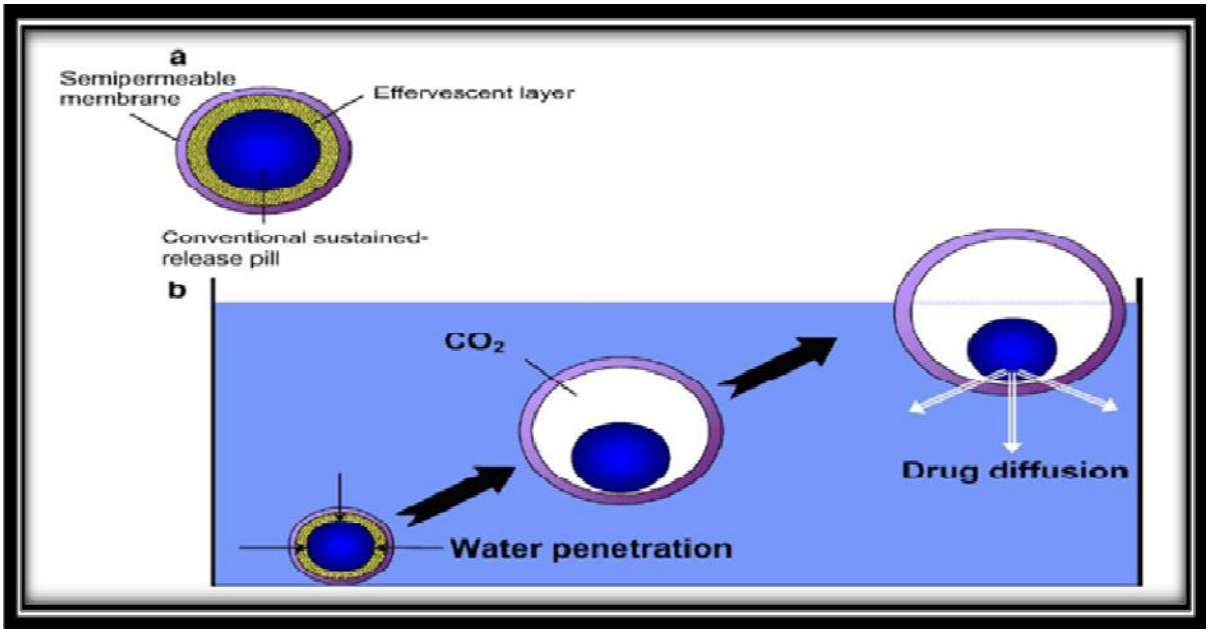

Fig. 3: Schematic representation of ‘‘floating pill’’ proposed by Ichikawa (a). The penetration of water into effervescent layer leads to a CO2 generation and makes the system float (b). Adapted from Ichikawa et al. Used with permission. [15]

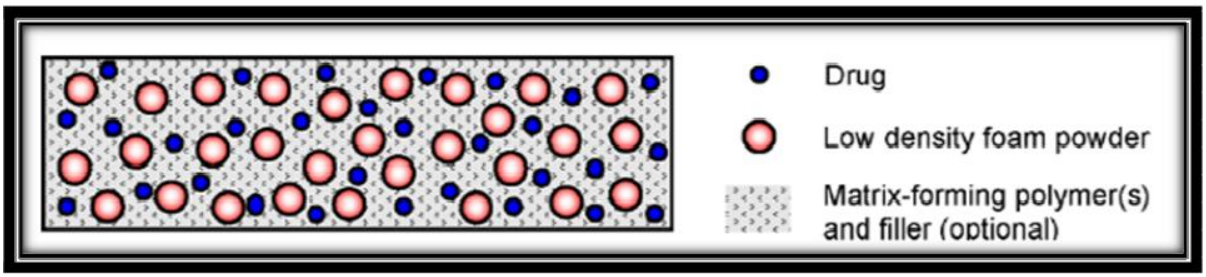

Fig. 4: Schematic presentation of the structure of the low-density, floating matrix tablets. Adapted from Streubel et al. Used with permission. [15]

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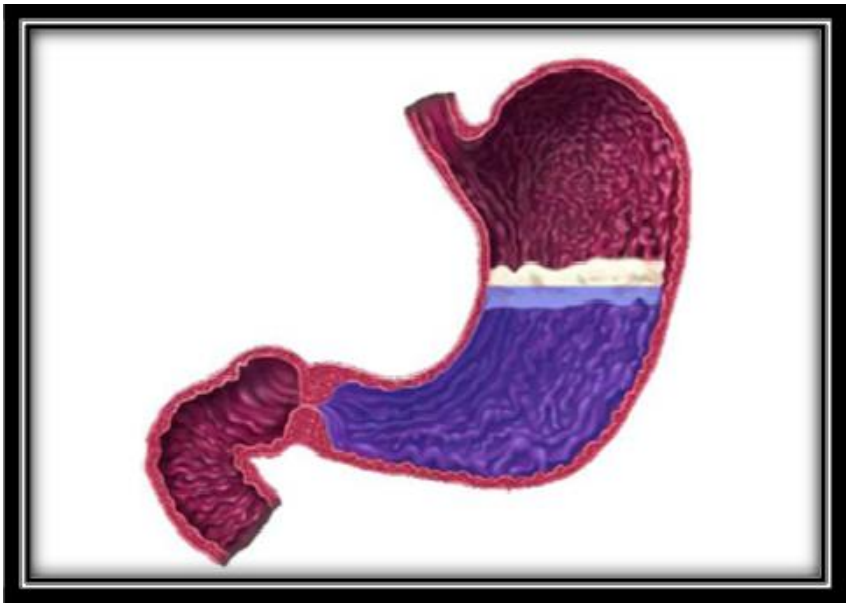

Fig. 5: Schematic illustration of the barrier formed by a raft-forming system[15]

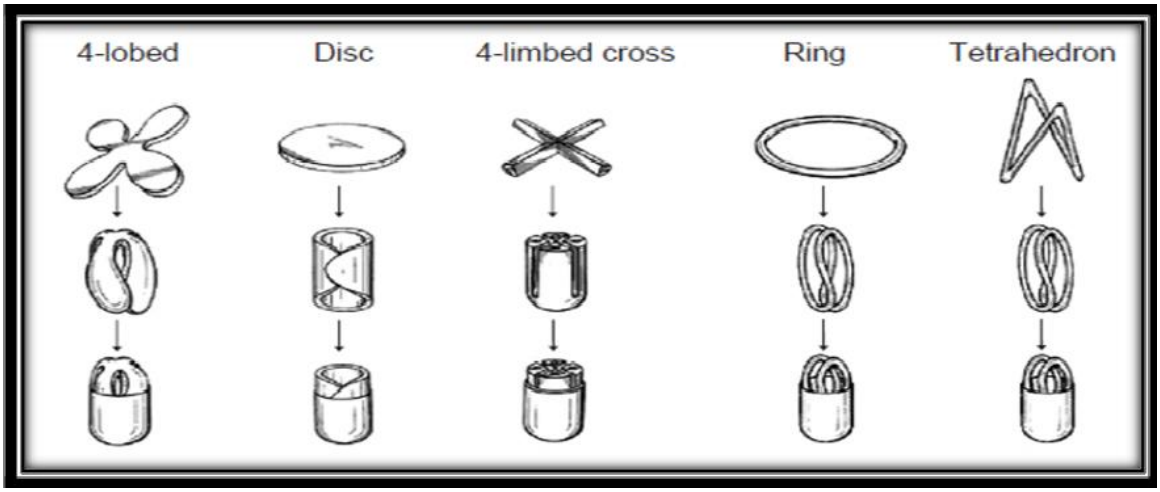

Fig. 6: Different geometric forms of unfoldable systems [15]

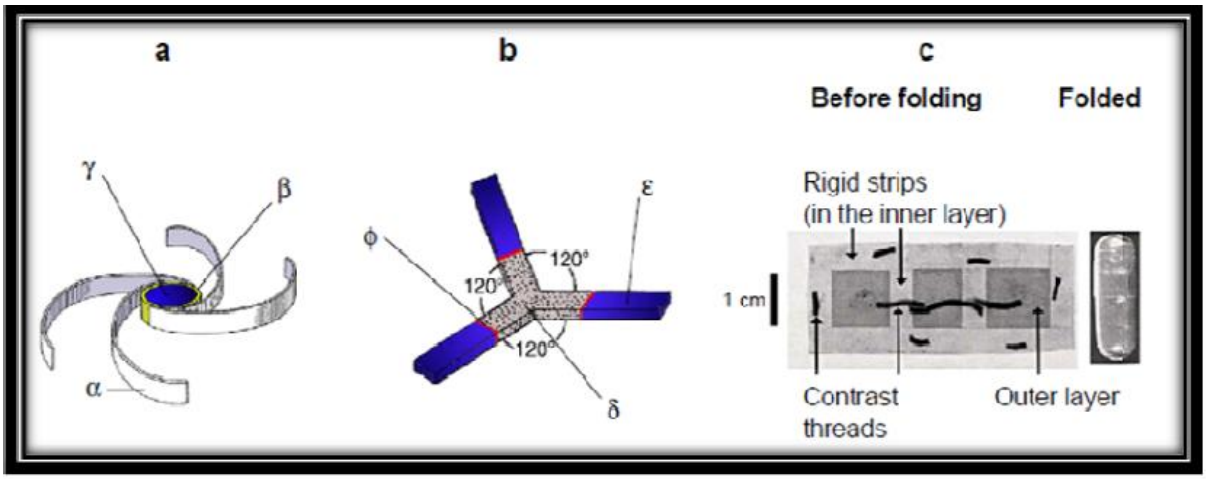

Fig. 7: Different unfoldabe systems. System partially unfolded a: retention arms, h: receptacle, g: controlled release tablet. Unfolding dosage form (b). y: shape memory material, (: erodible material, f: component connecting y and (Gastroretentive dosage form before and after (c). Used with permissions.[15]

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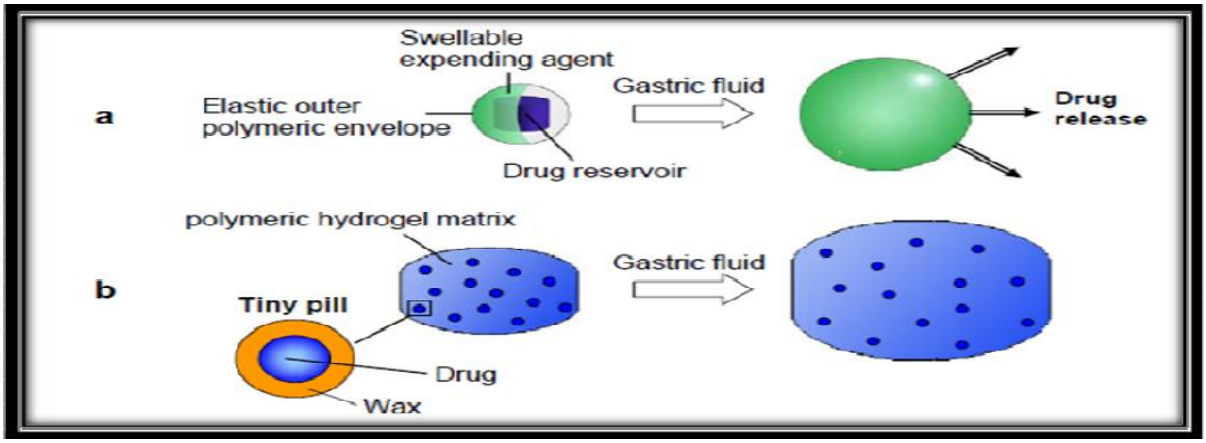

Fig.8: Swellable systems developed by Mamajek and Moyer (a) & Urquhart and Theeuwes (b). [15]

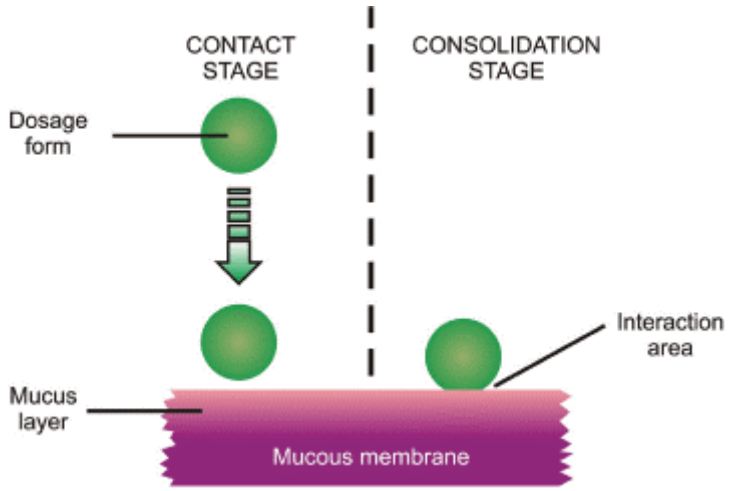

Fig.9: The two steps of mucoadhesion process.

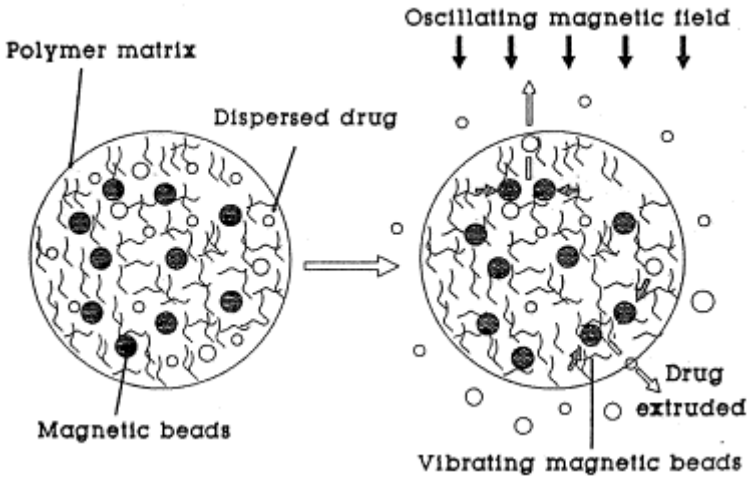

Fig.10: Mechanism of magnetic system.

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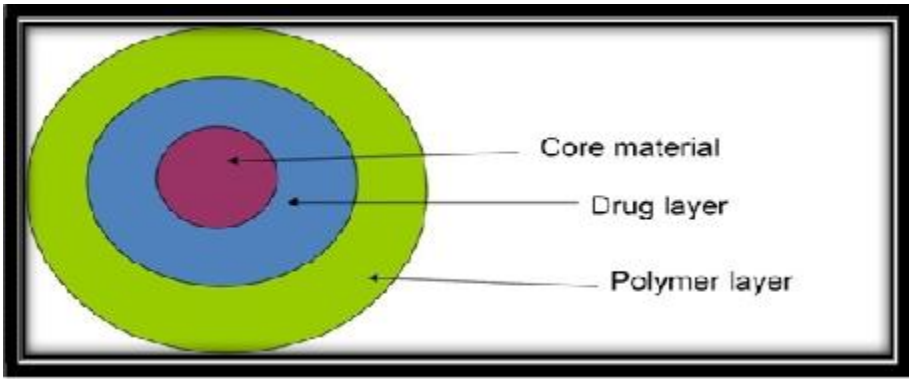

Fig. 11: Multiparticulate Drug Delivery Systems [12]

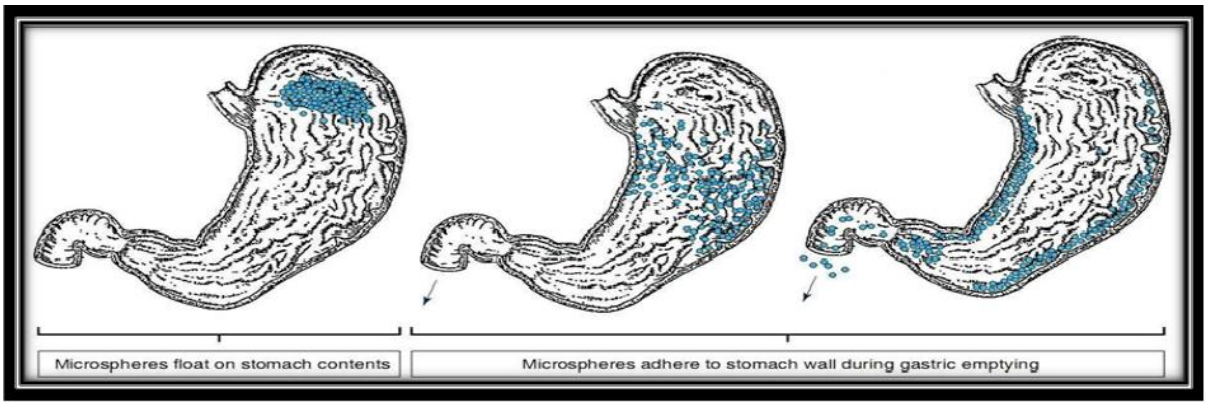

Fig. 12: Proposed mechanism for retention of microsphere in the human stomach[16]

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