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Review Article

MULTIPLE UNIT SYSTEM: AN APPROACH TOWARDS GASTRORETENTION

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ABSTRACT

Oral drug delivery is the most preferable route due to easy administration, patient compliance, flexibility in formulation and cost effectiveness. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Over the last few decades several gastro retentive drug delivery approaches have been designed and developed, including high density (sinking) systems, low density (floating) systems, mucoadhesive system, unfoldable, extendible or swellable systems, superporous hydrogel systems, magnetic systems etc. Multiparticulate systems consist of several discrete subunits each containing a portion of drug. Multiparticulate system consists of high density pellets, granules, beads, microballoons, microspheres, mini or micro tablets filled in to sachets, capsules or compressed in to tablets. Multiple unit systems are advantageous over single unit dosage forms due to less possibility of dose dumping and provide more uniform and predictable drug release profile. This review compiles of various types of gastro retentive drug delivery system with special focus on multiple unit gastro retentive systems their method of preparation as well as characterization.

Keywords: Multiple unit system, pellets, microballons, minitablets, beads.

INTRODUCTION

Oral drug delivery is the most preferable route of drug delivery due to easy administration, patient compliance, flexibility in formulation and cost effectiveness. It is most widely utilized route of administration among all the routes that are utilized for systemic delivery of drugs via pharmaceutical products of different dosage form. From immediate release to sites specific delivery, oral dosage forms have made a great progress.[1] Some drugs are not absorbed throughout the entire gastrointestinal tract but only in certain areas and to a different extent. Such drug candidates are known to exhibit "absorption window". Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window resulting in diminished efficacy of the administered dose. Formulation of oral controlled release systems thus has been a challenge to formulation scientists because of their inability to retain and localize the system in the specific region of the gastrointestinal tract. Prolonging the gastric retention time of such a delivery system is desirable for achieving greater therapeutic benefit of the drug candidate. Delivery of drugs at a specific region in gastrointestinal tract, with so called absorption window needs the development of gastro retentive dosage forms.[2] Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and significantly prolong the gastric retention time (GRT) of drugs. Prolonged gastric retention improves bioavailability, increases the duration of absorption, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine.[3] Various approaches proposed for gastroretention are high density systems, low density/floating systems, bioadhesive systems, expandable or swellable systems. Multi-particulate (MP) systems have several performance advantages over single unit dosage forms. After ingestion, MP units are released and spread uniformly along the gastrointestinal tract resulting in a consistent drug release with reduced risk of local irritation, have a more reliable *in-vivo* dissolution performance resulting in more uniform and predictable drug release, less chance of dose dumping and avoidance of inter or intra subject variability. In a multiparticulate drug delivery system, the dosage form of the drug is divided among several discrete units, in contrast to a single-unit dosage form. Multiparticulate system consists of high density pellets, granules, beads, microballoons, microspheres, mini or micro tablets filled in to sachets, capsules or compressed in to tablets.

Approaches to Gastroretention

Several approaches have been proposed to retain the dosage forms in the stomach. These methods include bioadhesive system, swelling system/expanding system, high density system and floating system. These can be either single unit or multiple unit system.

Single Unit Systems

Floating Systems

Floating drug delivery systems (FDDS) is one of the important approaches to achieve gastric retention to obtain

sufficient drug bioavailability. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration.[3] Properties should possess by FDDS:[4]

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 g/cm^3).
- It must form a cohesive gel barrier.

Floating systems can be classified as:

- Non-Effervescent systems
- Effervescent systems

Effervecsent Systems

Effervescent systems are formulated with the use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of system and making it float on the gastric fluid.[3] An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.[5] These effervescent systems further classified into two types:

- Gas Generating systems
- Volatile Liquid/Vacuum Systems

Gas-generating Systems

Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuation in plasma drug concentration.

Intra Gastric Bilayer Floating Tablets

These are also compressed tablet containing two layers i.e.

· Immediate release layer and

· Sustained release layer.

Upon coming in contact with gastric fluid the immediate release layer disintegrates leaving behind the sustained release layer which floats in gastric fluid releases the drug for prolonged period of time[6-7].

Volatile Liquid / Vacuum containing Systems

Intra gastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment.[6]

Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid.[6-7]

Intra gastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components: drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically salt. An osmotic pressure is then created which acts on the collapsible bag and in turn forces the bag reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.[8]

Non-Effervescent Systems

The non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, poly-methacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. This system is further classified as follows:

Single Layer Floating Tablets

They are formulated by intimate mixing of drug wit gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms[7].

Bilayer Floating Tablets

A bilayer tablet contain two layer immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach[7]

Bio-adhesive System

Bioadhesion is defined as an interaction between a biological substrate (eg. polymers) and the biological membrane. The mucoadhesive systems extend the GRT by adhering them to

the gastric mucous membrane. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated.[6] In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon coming in contact with gastric fluid. Bonding mediated adhesion may involve various mechanical or chemical bonds. Chemical bonds may involve covalent or ionic bonds or Vander-Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic or neutral.[9]

Swelling Systems

After being swallowed, these dosage forms swell to a large size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. These system when comes in contact with gastric fluid, the polymer imbibes water and swells.[6] The extensive swelling of the polymers is a result of the physical–chemical cross-links present in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of crosslinking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer. Thus to maintain a balance between swelling and dissolution an optimum degree of cross-linking is desired.[10]

Raft forming Systems

Raft forming systems upon coming in contact with gastric fluids forms a viscous gel, wherein each portion of the liquid swells, forming a continuous layer called "raft", this raft floats on gastric fluids because of a low density created by the formation of CO_2.[6] The system contains a gel-forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense to float on the gastric fluids.[11]

Multiple Unit Systems

Floating Pills

These systems consist of sustained release pills as 'seeds' surrounded double layers. The inner layer consists of effervescent agents while the outer layer is of swellable polymer membrane layer. When the system is immersed in gastric fluid medium at body temperature, it sinks at once and then forms swollen pills like balloons, which floats due to lower density. This lower density is due to generation and entrapment of CO_2 within the system.[1]

Microspheres / Microballoons

Hollow microspheres (micro-balloons) are 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 µm. The drug is either dispersed or entrapped throughout polymeric matrix. Floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Mechanism of drug release from the microspheres:

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

Diffusion

On contact with aqueous fluids in the gastrointestinal tract, 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.[11]

Methods of preparation of microspheres:

Solvent Evaporation Method

Floating multiparticulate dosage form can be prepared by solvent diffusion and evaporation methods to create the hollow inner core. For emulsion solvent evaporation, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

- Oil in water emulsion solvent evaporation technique

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 lead 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 oil emulsification solvent evaporation technique

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 co- dissolved 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 h to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the micro particles are separated by filtration through a Whatman filter paper, washed three times

with n-hexane, air dried for 24 h and subsequently stored in desiccators.

Emulsion Solvent Diffusion Method

In this method solution of polymer and drug in ethanol methylene chloride is poured into an agitated aqueous solution of poly (vinyl alcohol) that is thermally controlled at 40^0C.[12] 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 micro particles.[8]

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.[13] Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively.[8]

Bead System

Calcium alginate/ Pectinate beads

Freeze dried calcium alginate beads are produce by dropping sodium alginate solution into aqueous solution of calcium chloride. So due to chemical reaction named as Ion tropic gelation. Elation take place and forms solid spherical gel beads, which are separated from solution and they are freeze dried at - 40^oC for 24 hours. The resultant weight of beads is less giving buoyancy up to 12 hours.[2] Similar to alginate, pectin can also be use for preparing gel beads, Combination of both means calcium-alginate-pectinate gel bead also tried, which gives fasten drug release as compare to only calcium pectinate beads. Calcium alginate beads also prepared with incorporation of Chitosan polymer so that it can incorporate air in beads.

Calcium Alginate Beads With Air Compartment

These are also calcium alginate beads but the difference is that the calcium alginate core is separated by air compartment from a coating membrane calcium alginate or mixture of calcium alginate and PVA. During the preparation of calcium alginate beads before drying process the beads are coated with the coating solution which may be calcium alginate or mixture of calcium alginate and PVA, and then they are dried. So that due to shrinkage of internal core bead during drying it produces the air compartment which imparts buoyancy. PVA is incorporated in coating mixture for improving membrane permeability as PVA is water soluble additive cause the leaching from membrane and making pores in membrane.[14]

Oil entrapped Gel Beads

Vegetable oil is use as floating carrier as they are light weight and hydrophobic used for floating by incorporating it into gel matrix of beads. Oil entrapped beads are prepared by both calcium alginate bead and calcium pectinate beads. Pectin has some emulsification property, so aqueous solution of pectin is mixed with edible oil. Emulsion is obtained by homogenization. And this emulsion is extruded into calcium chloride solution to form beads which are separated, washed and dried.[15]

Ion Exchange Resins

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.[16]

Pellets

Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. These pellets usually range in size from 0.5-1.5 mm and in some cases may be as large as 3.0 mm[17-20]. Method of preparation of pellets is as follows:

- Compaction
- Agitation
- Layering
- Globulation

Compaction

It is the most widely used two step process utilized to prepare denser pellets. The steps are as follows:

i) Compression ii) Extrusion-spheronization

Compression

In this technique, particles are prepared by dry blending or wet granulation process and are further subjected to drying. Thus the particles rearrange themselves to form a closely packed mass retaining most of their original properties.

Extrusion-Spheronization

Wet mass is prepared by using binding solution or hot melt wax. Wet mass is then shaped using different type's extruders. Extrudate is then broken to produce particles which are then shaped into spheres using spheronizer. Drying of the pellets at room temperature or at an elevated temperature in the fluidized-bed drier, in an oven, in a forced circulation oven or in a microwave oven

Agitation

It is a pelletization process in which the powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures are converted to spherical particles by a continuous rolling or tumbling action. It is also known as spherical agglomeration. Spherical agglomeration can be either done by liquid-induced and melt-induced process. In liquid-induced agglomeration process, liquid is added to the powder before or during the agitation step. As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges subsequently replaced by solid bridges, derived from the hardening. Binder or any other dissolved material within the liquid phase. The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets. Melt-induced agglomeration processes are similar to liquid-

induced process except that the binding material is a melt. Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-based liquid bridges.

Globulation

Spray drying and spray congealing are known as globulation processes. Spray drying involves atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. During spray drying, drug in solution or suspension form are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the solvent medium is initiated. Thus drying continues until solid particles are formed. Generally, spray-dried pellets tend to be porous. During spray congealing, a drug substance is allowed to melt, disperse, or dissolve in hot melts of waxes, fatty acids, etc., and sprayed into an air chamber, where the temperature is below the melting temperatures of the formulation components, to provide spherical congealed pellets under appropriate processing conditions. A critical requirement in a spray congealing process is that the formulation components have well-defined, sharp melting points or narrow melting zones. Because the process does not involve evaporation of solvents, the pellets produced are dense and non-porous.

Layering technique

Layering results in heterogeneous pellets with a core and a shell. For this process, seed or starting core material is required.

Powder layering

During powder layering, a binding solution and a finely milled powder are added simultaneously to a bed of starter seeds at a controlled rate. In the initial stages, the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed liquid. Fluidized bed dryer is used in order to ensure rapid drying. The core particles (seeds) are fluidized in a warm or hot air stream. A binding liquid is sprayed and simultaneously add the drug substance as a powder. The particles stick to the wetted surface of the seed material and form a layer together with the binder after drying.

Solution/ Suspension layering

Solution/suspension layering involves the deposition of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug. The process continues until the desired quantity of the pellets is achieved.

Minitablets

The production of mini-matrices using a tableting technique is an attractive alternative to the production of pellets, as the presence of solvents (e.g. water) is avoided and high production yields are obtained. The normal size of mini tablets are with a diameter of 3 mm. Formulating mini-tablets using tableting technique has advantages over pellets, as it does not require any solvents for its production, defined size and strengths can easily be produced with good batch to batch uniformity.[17] Mini tablets filled into hard capsules, after disintegration, release these subunits as multiple dosage forms.[21] Two approaches proposed for formulation of minitablets:[22-25]

A biphasic system with multiple-unit mini-tablets based on gas formation technique

The system consists of loading dose as uncoated core units, and prolonged release core units are prepared by direct compression process. The prolonged release core units were coated with three successive layers, one of which is seal coat, an effervescent seal coat (sodium bicarbonate), and an outer polymeric layer of polymethacrylates.[17]

A novel approach based on non-effervescent technique in which consists immediate release mini-tablets (IRMT) and sustained-release minitablets (SRMT) in a hydroxypropyl methylcellulose (HPMC) capsule. The immediate-release mini-tablets contains drug, excipients and low-substituted hydroxypropyl cellulose (a disintegrant), and the tablets were coated with HPMC, a water-soluble polymer to release the content immediately after coming in contact with gastric fluid. The sustained release minitablets contained only drug and excipients, and were coated with a mixture of HPMC and the water-insoluble polymer ethylcellulose. The release profile of drug for the SRMT could be controlled by varying the thickness of the coat, and the lag time could be controlled by varying the amount of ethylcellulose present in the polymer coat.[22]

Characterization of Multiple Unit Systems

Characterization of Microspheres

Micro-meritic properties

Floating microspheres are characterized by their micromeritic properties such as angle of repose, tapped density, compressibility index, true density and flow properties. True density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method. The hollow nature of microspheres is confirmed by scanning electron microscopy[11]. The compressibility index is calculated using following formula:

$$I = Vb - Vt / Vb \times 100$$

Where, Vb is the bulk volume and Vt is the tapped volume.

Particle size and shape

Scanning electron microscopy (SEM) provides higher resolution in contrast to the light microscopy (LM). The most widely used procedures to visualize micro particles 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 multiparticulate surfaces and after particles are cross sectioned, it can also be used for the investigation of double walled systems. Coulter counter are other than instrumental methods, which can be used for the characterization of size, shape and morphology of the multiparticulates.

Floating behavior

Appropriate quantity of the floating micro particulates is placed in 100 ml of the simulated gastric fluid (pH 1.2) and the mixture is stirred with a magnetic stirrer. The layer of

buoyant micro particulate is pipetted and separated by filtration. Particles in the sinking particulate layer are separated by filtration. Particles of both types are dried in a desiccator until constant weight is achieved. Both the fractions of microspheres are weighed and buoyancy is determined by the weight ratio of floating particles to the sum of floating and sinking particles.

Buoyancy (%) = Wf / Wf + Ws

Where, Wf and Ws are the weights of the floating and settled micro particles.

Entrapment efficiency

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

% Entrapment = Actual content/Theoretical content x 100

***In-vitro* drug release studies**

The release rate of floating microspheres is determined using United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug is filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution apparatus. 500 ml of the SGF containing 0.02 % w/v of Tween 20 is used as the dissolution medium. The dissolution fluid is maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5 ml samples are withdrawn at each 30 minutes 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 is maintained by adding 5 ml of fresh dissolution fluid after each withdrawal.

***In-vivo* Studies**

The *in-vivo* floating behavior can be investigated by X-ray photography of hollow micro particulate loaded with barium sulphate in the stomach of beagle dogs. The *in-vitro* drug release studies are performed in a dissolution test in a dissolution media. The *in-vivo* plasma profile can be obtained by performing the study in suitable animal models.

Characterization of Pellets

Apart from micromeritic properties pellets are characterized for the following[17]:

Shape analysis

At least 50 pellets from each batch are randomly selected for shape analysis. The pellets were mounted on a light microscope fitted to a Camera Lucida and the images of the pellets were drawn manually on a graph paper. The area of the images (A) and the maximum and minimum radius are calculated from which the various shape factors are calculated as per the following formulae

Aspect Ratio = d_{max} / d_{min}

Where, dmax and dmin are maximum diameter and minimum diameter of the pellets respectively.

Friability

The tendency of the pellets to flake off during handling resulting in the formation of dust is assessed by rotating the pellets in a friabilator or by shaking the pellets in a Turbula mixer for a fixed period of time. Both techniques make use of glass beads to increase the mechanical stress on the pellets.

Wettability

Pellet is placed on clean glass slide. A 15 µl drop of distilled water is placed carefully with the help of a micro-syringe on the pellet. Photographic impressions of the water drop in contact with the pellet are recorded in the static stage.

Scanning electron microscopy (SEM)

The morphology of pellets is examined by scanning electron microscopy. Samples are freeze dried, cross sectioned and then placed onto aluminum stubs coated with adhesive. The cross-sections of the pellets are coated with gold under vacuum and examined under the microscope to visualize the surface characteristics of the pellets.

Moisture Content

Moisture content is determined by means of Karl Fisher titration.

Content uniformity

Content uniformity (assay) is performed for each batch as per the procedure given in the official pharmacopoeia.

Characterization of Mini tablets

Mini tablets are characterized for it shape and size distribution, weight variation, hardness, % friability, angle of repose, Carss's index, Hauser's ratio, flowability, disintegration, *in vitro* dissolution testing and SEM[22-25].

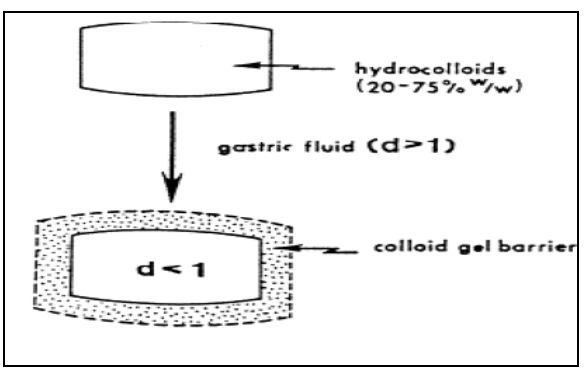

Figure 1: Intra Gastric Single Layer Floating Tablets

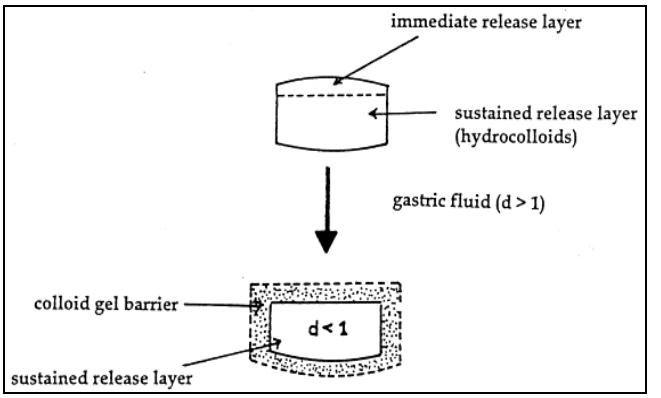

Figure 2: Intra Gastric Bi layer Floating Tablet

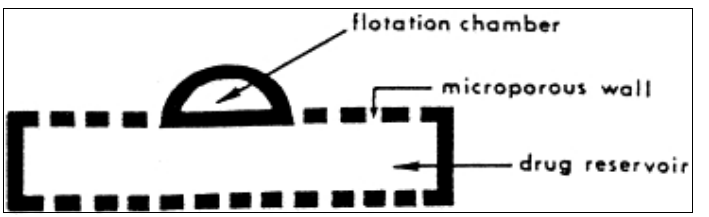

Figure 3: Intra gastric Floating Gastrointestinal Drug Delivery System

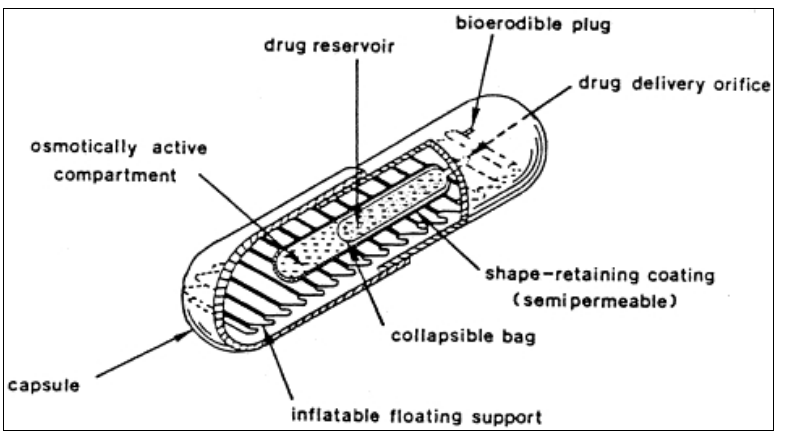

Figure 4: Intra gastric Osmotically Controlled Drug Delivery System

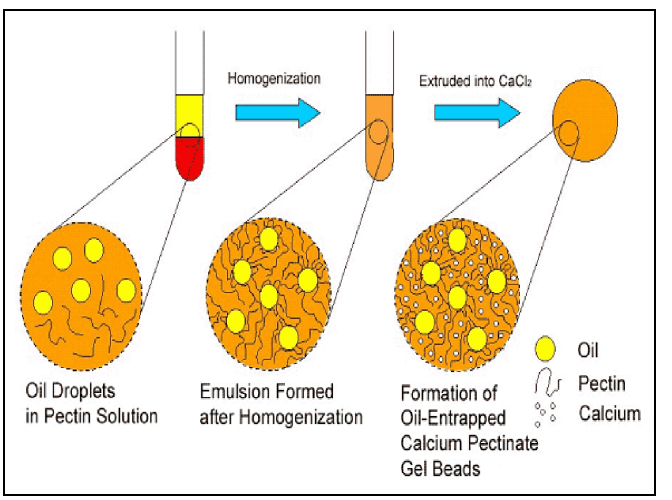

Figure 5: Oil Entrapped Gel Beads

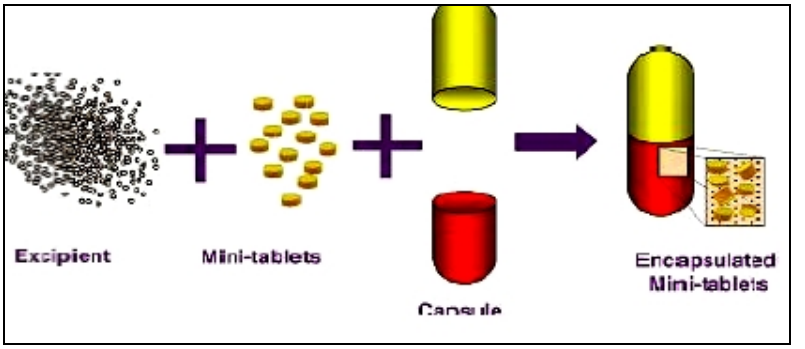

Figure 6: Mini tablets Filled Into Capsule

CONCLUSION

Multiparticulate gastro retentive drug delivery systems are proving a promising approach to retain drugs in stomach which exhibits narrow absorption window. These delivery systems can target drugs to specific sites for both local as well as systemic effects and with desired drug release profile thus improving bioavailability of many drugs.

REFERENCES

1. Jamil Faraz, Kumar Sunil, Sharma Saurabh, Vishvakarma Prabhakar and Singh Lalit. Review on Stomach Specific Drug Delivery Systems Development and Evaluation. International Journal of Research in Pharmaceutical and Biomedical Sciences 2011; 2(4): 1427-1433.
2. Dixit Nikita. Floating Drug Delivery System: Journal of Current Pharmaceutical Research 2011; 7(1): 6-20.
3. Garg R, Gupta GD. Progress in Controlled Gastroretentive Delivery Systems. Tropical Journal of Pharmaceutical Research 2008; 7(3): 1055-1066. http://dx.doi.org/10.4314/tjpr.v7i3.14691
4. Chien YW. Novel drug delivery system, Marcel Dekker, 2nd ed. Rev. Expand; p. 139-196.
5. Shukla Shruti, Patidar Ashish, Agrawal Shikha, Choukse Raju. A Review On: Recent Advancement of Stomach Specific Floating Drug Delivery System. International Journal of Pharmaceutical and Biological Archives 2011; 2(6): 1561-1568.
6. Soni Ravi P, Patel Ashish V, Patel Rahul B, Dr Patel MR, Dr Patel KR, Dr Patel NM. Gastro retentive Drug Delivery Systems: A Review. International Journal of Pharma World Research 2011; 2(1).
7. Singh Sanjay, Joshi Vaibhav and Barpete Pravin Kumar: Gastroretentive Drug Delivery System: Current Approaches. Journal of Pharmacy Research 2009; 2(5): 881-886.
8. Pujara Naisarg D, Patel Namrata V, Thacker Ankita P, Raval Brahmdutta K, Doshi Sumit M, Parmar Ramesh B. Floating Microspheres: A Novel Approach for Gastro Retention. World Journal of Pharmacy and Pharmaceutical Sciences 2012; 1(3): 872-895.
9. SU Zate, PI Kothawade, GH Mahale, KP Kapse, SP Anantwar. Gastro Retentive Bio adhesive Drug Delivery System: A Review. International Journal of Pharm Tech Research 2010; 2(2): 1227-1235.
10. Santosh Shep, Sham Dodiya, Lahoti Sandeep, Mayee Rahul. Swelling System: A Novel Approach towards Gastro retentive Drug Delivery System. Indo-Global Journal of Pharmaceutical Sciences 2011; 1(3): 234-242.
11. Ramana Jaspreet, Kawatra Monica, Jain Upendra. Recent Advances in Floating Microspheres as Gastro-Retentive Drug Delivery System: A Review. International Journal of Recent Advances in Pharmaceutical Research 2012; 2(3): 5-23.
12. Niranajan Patra *et. al.* Floating Microspheres: Recent Trends In Development Of Gastroretentive Drug Delivery System. International Journal of Pharmaceutical Sciences and Nanotechnology 2011; 4(1): 1296-1306.
13. Sivannarayana P, Saikishore, Prameela Rani, Veda Pravallika, Venu Babu. A Review on Novel Approach in Gastro Retentive Floating Drug Delivery: Floating Microspheres. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2012; 3(3): 1279- 1299.
14. Patel Nirav, Nagesh C, Chandrashekhar S, Patel Jinal and Jani Devdatt. Floating drug delivery system: An innovative acceptable approach in Gastro retentive drug delivery. Asian J. Pharm. Res 2012; 2(1): 07-18.
15. Pornsak Sriamornsak, Panida Asavapichayont, Jurairat Nunthanid, Manee Luangtana-anan, Sontaya Limmatvapirat and Suchada Piriyaprasarth. Wax-incorporated Emulsion Gel Beads of Calcium Pectinate for Intragastric Floating Drug Delivery. AAPS Pharm Sci Tech 2008; 9(2): 571-576. http://dx.doi.org/10.1208/s12249-008-9082-4
16. Kunal P Nayak, Pratik Upadhyay, Jayant Deshpande Arohi R Valera, Chauhan Nirav P. Gastro retentive Drug Delivery Systems Recent Approaches: A Review. Journal of Pharmaceutical Research and Opinion 2011; 2(1): 1–8.
17. Bhavik Solanki, Patel Rutvik, Bhavesh Barot, Parejiya Punit and Pragna Shelat. Multiple Unit Dosage Forms: A Review 2012; 1(1): 11-21.
18. Isaac GS, Axel K. Pelletization Techniques. In: James Swarbrick. Encyclopedia of pharmaceutical technology. 3rded. New York, Informa healthcare 2007; 4: 2651- 2663.
19. Klaus K, Prof Peter K. Pharmaceutical pellets: Definition, properties, production; Ex Act 2005; 15: 2-5.
20. Jamila Hamdani, Andre J Moes, Karim Amighi. Development and *In vitro* Evaluation of A Novel Floating Multiple Unit Dosage Form Obtained By Melt Pelletization. International Journal of Pharmaceutics 2006; 322: 96–103. http://dx.doi.org/10.1016/j.ijpharm.2006.05.052
21. Mohd Abdul Hadi, Raghavendra Rao. Novel Technologies In Formulations: An Overview. World Journal of Pharmaceutical Research 1(3): 415-431.
22. Makoto I, Kenichi A, Minoru H, Masao K. A novel approach to sustained pseudoephedrine release: Differentially coated mini-tablets in HPMC capsules. Int J Pharm 2008; 359(1-2): 46-52. http://dx.doi.org/10.1016/j.ijpharm.2008.03.034
23. Dr Hindustan Abdul Ahad, Anusha N, Naresh Babu G, Anil Kumar. Fabrication and *in vitro* evaluation of Venlafaxine Hydrochloride mini tablets filled hard Gelatin Capsules. International Journal of Current Trends in Pharmaceutical Research 2013; 1(3): 161-168.
24. Noorana Tehseen, Vinay Rao, Mohd Abdul Hadi. Design and Characterization of Twice Daily Mini-Tablets Formulation of Pregabalin. International Journal of Pharmacy And Pharmaceutical Sciences 2013; 5 (Suppl 1): 168-175.
25. NG Raghavendra Rao, Mohd Abdul Hadi, Harsh A Panchal: A Novel Approach to Sustained Montelukast Sodium Release: Differentially Coated Mini-Tablets In HPMC Capsules. Int J Pharm Biomed Res 2011; 2(2): 90-97.
26. Parmar Kunal Vinodbhai, MC Gohel, RK Parikh B, Shital Bariya, Rajeshvari N Suthar. Sustained Release Floating Microspheres of Acyclovir: Formulation, Optimization, Characterization And *In Vitro* Evaluation. International Journal of Drug Development and Research 2011; 3(1): 242-251.
27. Gattani YS. Floating Multiparticulate drug delivery systems: an overview. International Journal of Pharma and Bio Sciences 2010; (2): 1-14.
28. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating Drug Delivery Systems: A Review**.** AAPS Pharm Sci Tech 2005; 06(03): E372-E390. http://dx.doi.org/10.1208/pt060347
29. Gaba Punam. Floating micro spheres: A Review. Pharmainfo.net 2008; 6(5).

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