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International Journal of Pharmaceutical and Biological Science Archive 2 (5) 2014, 09-22

REVIEW ARTICLE

NOVEL APPROACH IN GASTRO RETENTIVE DRUG DELIVERY SYSTEM: FLOATING MICROSPHERES

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ABSTRACT

There are many technique delivering a therapeutic substance to the target site in a sustained or controlled release fashion 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 hydro dynamically balanced systems (HBS), Gatsroretentive drug delivery system offers several advantages besides providing better bioavailability to poorly absorbed drugs and a required release profile thus attracting interest of pharmaceutical formulation scientists. A large number of marketed formulations are formulated as gastro retentive dosage forms. Floating microspheres is one among the several approaches to gastro retention, like mucoadhesion, flotation, sedimentation, expansion, modified shape systems etc. These systems are useful in overriding the several problems encountered during the development of a pharmaceutical dosage forms. The intention of this review is to focal point on the recent advances in the field of preparation, characterization, evaluation and applications of floating microspheres in the area of gastro retentive dosage forms. The review also highlights the advantages with reference to the multi-particulate systems, as well as provides an overview of the future prospective that can take place in this area.

Key words: Gastro-retention, FDDS, floating microspheres, multi-particulates

INTRODUCTION:

The gastrointestinal tract can be divided into three main parts.

They are namely: Stomach, Small intestine—duodenum, jejunum and ileum and Large intestine.

The GIT (gastrointestinal tract) is a continuous muscular tube, extending from the mouth to the anus. The GIT is like a tube of 9 m long that starts from the mouth & ends with the anus. The function is to take in nutrients and eliminate waste by such physiological processes such as secretion, motility, digestion, absorption and excretion. The walls of the GIT, from the stomach to the large intestine, have different layers of tissue from outside to inside. The stomach has a third muscle layer known as the "oblique muscle layer" which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body The different smooth musde layers are responsible for performing the motor functions of the GIT, i.e. gastric emptying and intestinal transit. The stomach is a located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastria and left hypochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum Since the drugs are absorbed in the upper small intestine, it will be beneficial to develop the dosage forms that reside in that region.

The stomach is divided into 3 anatomical regions:

1. Fundus
2. Body
3. Pylorus (antrum)

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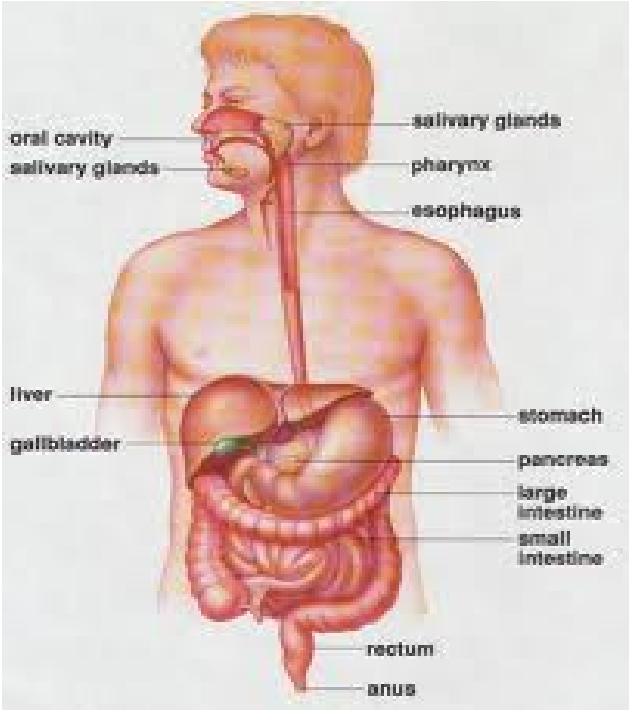

Figure 1: Anatomy of GIT

The proximal part is made of fundus, body acts as a reservoir for undigested material & antrum acts as a pump for gastric emptying by propelling actions. Antrum is a major site of mixing. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to the small intestine

Physiology of the stomach:

The GIT is always in a state of continuous motility. There are two modes of motility pattern such as (a) the digestive mode and (b) inter digestive mode. Gastric emptying occurs during fasting as well as fed states. In case of fasted state an inter digestive series of electrical events occurs in cydic manner both through the stomach and the small intestine every 2–3 h. This electrical activity is called as inter digestive my electric cyde or migrating myelectric complex (MMC) the migrating my electric complex (MMC) is further divided into

Four phases.

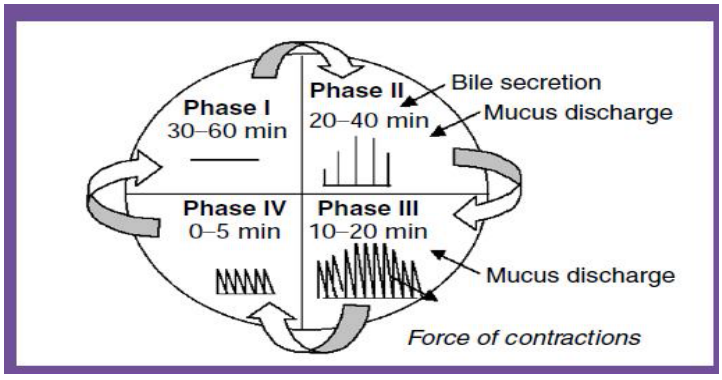

Figure 2: Motility pattern of GIT

PHASE I:

It is quiescent period with rare contraction & lasting from 30 to 60 min.

PHASE II:

It consists of intermittent action potentials & contraction that gradually increases intensity & frequency as the phase progresses.

It lasts for 20–40 min.

PHASE III:

It is for short period of intense, large regular contraction from 10 to 20 min, and it sweeps the undigested material from the stomach to the small intestine. Phase III is termed as 'housekeeper wave' as it enables to sweep away all undigested materials out of the stomach & down

to the small intestine. Between phase III & phase I of two consecutive cycles a brief transitional phase IV occurs.

PHASE IV

Short transitional phase of about 0 to 5 min. In fed state gastric emptying is slow. The motor activity in the fed state is induced 5–10 min after ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2–6 h. When GRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric retention time (GRT) and transit time in the gastrointestinal tract.

Factors controlling the gastro retentive drug delivery system:

There are various factors to be considered for the development of gastro retentive dosage forms formulation to prolong the dosing intervals and thus improve patient compliance. They are shown below.

Factors related to the dosage forms;

Size of the dosage form:

To allow the dosage form to pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. In most cases, the larger the dosage form the greater will be the GRT. Due to the larger size of the dosage form, it could not quickly pass through the pyloric antrum into the intestine. Small-size tablets leave the stomach during the digestive phase while the large-sized tablets are emptied during the housekeeping waves.

Shape of dosage form:

Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared to other shapes

Density of dosage form:

Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to the bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of b1.0 g/cm3 is required to exhibit floating property.

However the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium

Food intake and its nature:

Fed & unfed state:

Under fasting condition under fasting conditions, the gastrointestinal motility is characterized by periods of strong motor activity or MMC that occurs every 1.5 to 2 h. The MMC sweeps the undigested material from the stomach and if the timing of administration of the dosage form coincides with that of the MMC, the Gastric retention time of the unit can be predictable to be very short. However, in the fed state, MMC is postponed and Gastric retention time is considerably longer

Food intake & nature of food:

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract influences the gastric retention time of the dosage form. Usually

The presence of food in the gastrointestinal tract improves the gastric retention time of the dosage form & thus, the absorption of drugs increases by allowing its stay at the absorption site for a longer period.

Calorie content:

The rate of gastric emptying primarily depends on the caloric contents of the ingested meal. It does not differ for proteins, fats, carbohydrates as long as their caloric content is the same. Generally an increase in acidity, osmolarity, and caloric value slows down gastric emptying GRT can be increased between 4 and 10 h with a meal that is high in proteins and fats.

Frequency of feed:

The GRT can increase by more than 400 min when successive meals are given compared with a single meal due to the low frequency of MMC.

Patient related factors:

Gender:

Gastric emptying rate may differ in male & female. Generally the gastric emptying in women was slower than in men.

Age:

Elderly people, especially those over 70 years have a longer gastro retentive time. Thus gastric emptying time is slowed down

Posture:

The effect of posture on GRT, found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, insupine position, the floating units are emptied faster than the non floating units of similar size.

Concomitant drug administration:

Administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g.

codeine) and prokinetic agents (e.g. metoclopramide, cisapride) can alter gastro retention of oral dosage forms Anticholinergic like atropine and propantheline increase gastric residence time. Drugs like metoclopramide and cisapride decrease gastric residence time. In gastric ulcer, diabetes, and hypothyroidism there is an increase in gastric residence time. In the case of hyperthyroidism and duodenal ulcers there is a decrease in gastric residence time

Volume of the GI fluid:

The resting volume of the stomach is 25 to 50 ml. The volume of Liquids administered affects the gastric emptying time. When the volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

Effect of gastrointestinal fluid:

On comparison of the floating and non-floating units, it was concluded that regardless of their sizes the floating units remained buoyant on the gastric contents throughout their residence in the GIT, while the non-floating units sink and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during the digestive phase while non-floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase

Different Gastro retentive form:

Many technological approaches have been made to develop a dosage form that can be retained in the stomach. The gastro retentive forms that have been proposed to increase the retention of an oral dosage form in the upper part of the GIT are described into

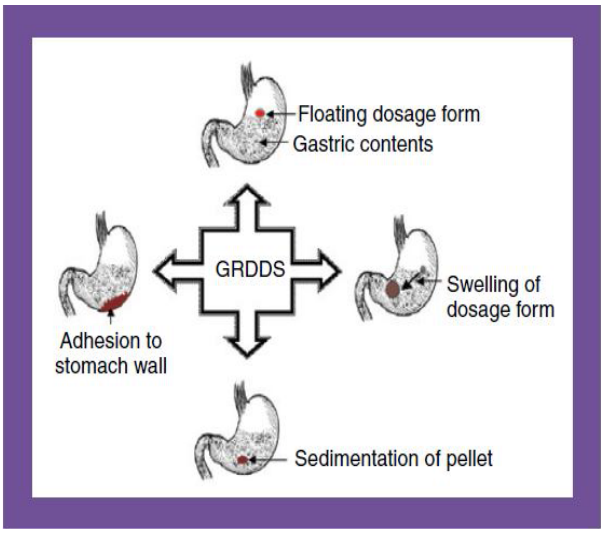

Figure 3: Different gatsroretentive forms.

High-density systems/non-floating system:

Gastric contents have a density close to water (˜ ≈ 1.004 g/cm3).

These systems have density higher than the gastric content. A density dose to 2.5 g/cm3 is necessary for significant prolongation of gastric residence time. Barium sulfate, zinc oxide, iron powder, and titanium dioxide are excipients used to formulate such type of dosage Form.

Low density system/floating system:

Floating systems were first described by Davis in 1968. Floating drug delivery system has bulk density lower than that of the gastric fluid, and thus stays buoyant in the stomach for an extended period. Floating drug delivery system is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine. On the basis mechanism of buoyancy two specifically different technologies, are non-effervescent

and effervescent systems have been used for the development of the floating drug delivery system.

Non effervescent system:

The non-effervescent floating drug delivery system is based on the mechanism of swelling of polymer or bioadhesion to mucosal layer in the GI tract. Non-effervescent floating dosage forms use a gel forming or swell able cellulose type of hydrocolloids, polysaccharides, and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylates, and polystyrene. The preparation methods of such dosage forms involve the addition of the drug with a polymer, which swells in contact with the gastric fluid and maintains a relative integrity of shape and a bulk density is less than the outer gelatinous barrier.

Single layer floating tablets:
They are formulated by uniform mixing of a drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains specific gravity less than one. They are formulated by blending of a drug with low-density enteric materials such as cellulose acetate phthalate and hydroxyl propyl methyl cellulose.

Bi-layer floating tablets:
A bi-layer tablet contains two layers. One is an immediate release layer which releases loading dose from the system while the other is a sustained release layer which releases dose by absorbing gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintains a specific gravity less than unity and thereby remains buoyant in the stomach

Hydrodynamically balanced systems:
Were the first to designate these 'Hydrodynamically balanced systems. These are single-unit dosage forms, containing one or more gel forming hydrophilic polymers. Hydroxy propyl methylcellulose (HPMC) is the most common used excipients, although hydroxyl ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC), sodium carboxy methylcellulose (NaCMC), agar, carrageen or alginic acid is also used. The polymer is mixed with a drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produce a floating mass. Modopar LPR, based on HBS system was marketed during the 1980s

Microballoons/hollow microspheres:
Microballoons/hollow microspheres loaded with drugs in their other polymer were prepared by simple solvent evaporation or solvent diffusion methods to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio.

Drug Candidates Suitable for Floating Drug Delivery:
Drugs which have site-specific absorption in the stomach or upper parts of the small intestine (furosemide, riboflavine-5- phosphate), drugs required to exert local therapeutic action in the stomach (antacids, anti-H.pylori agents, misoprostol), drugs unstable in the lower part of Gastro-intestinal tract (captopril), drugs insoluble in intestinal fluids (quinidine, diazepam), drugs with variable bioavailability (satolol HCl)

Polymers used for floating drug delivery system:
For more than two decades, considerable use of polymeric materials to deliver bioactive agents has attracted attention of various investigators throughout the scientific community.
Of drug to a specific region in the gastrointestinal tract i.e. stomach. Both synthetic and
Natural polymers have been studied widely in the preparation of drug delivery systems. In spite of the advent of many synthetic polymers, use of natural polymeric materials has gained lot of importance during the last two decades in drug delivery arena. Incorporation of natural polymers in various drug delivery systems looks to be an active avenue of research and development due to obvious reasons of compatibility, inexpensive and ready availability. These polymers, particularly with pronounced swelling properties have been frequently employed in the formulation of different gastro retentive products.

Natural Polymers:
Albumin, Collagen, Gelatin, Fibrinogen, Casein, Fibrin, Polylactic acid Chitin, Chitosan
Hyaluronic acid, Starch, Dextrose, Dextran, Alginic acid.

Synthetic Polymers:
Polylactic/glycolic acid, Poly (β-hydroxybutyric acid), Poly caprolactone, Polyanhydrides

Sr. No.	POLYMER	MECHANISM
	Modified starch, HPMC, Carbopol 974P	Slower release of drug
	Ethyl Cellulose	Controlled release for longer period of time
	PLGA, Chitosan	Vaccine delivery
	PLA, PLGA, Starch, Cyanoacrylate etc	Drug delivery without toxic side effects
	Chitosan coated PlGA microspheres	Targeted drug delivery
	Polyvinyl alcohol, polyacrylamide	Adsorption of harmful substances in blood
	Magnetic polystyrene microspheres	Specific cell labeling
	Polymer resins such as Agarosepolyacroline, sephadex	Affinity chromatography

Table 1: Different polymers with their mechanism

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

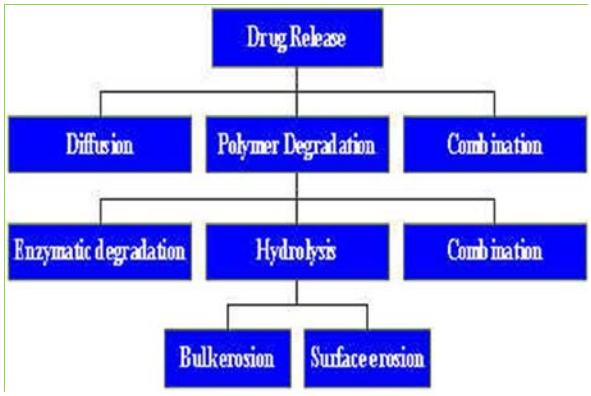

Figure 4: Mechanism of floating microspheres

Methods used of preparation of microspheres:
1. Solvent evaporation method
a. Single emulsion technique
b. Double emulsion technique
2. Coacervation phase separation method
3. Spray drying and spray congealing method
4. Polymerization method

1. Single emulsion technique:
The micro particulate carriers of natural polymers 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. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, di acid chloride etc. Heat denaturation is not suitable for thermo labile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation.

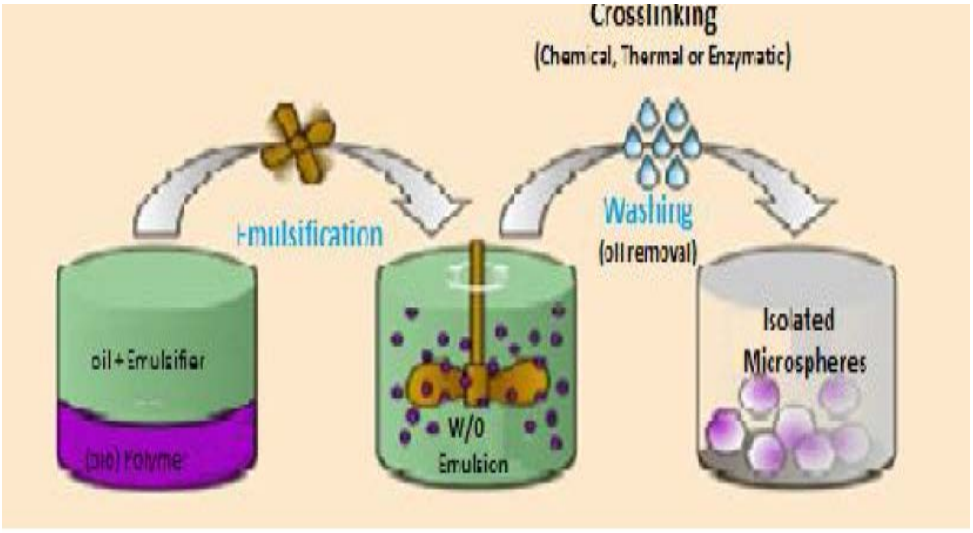

Figure 5: Single emulsion technique

2. Double emulsion technique:

Double emulsion method of microspheres preparation involves the formation of the multiple

Emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results solution forms the double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction.

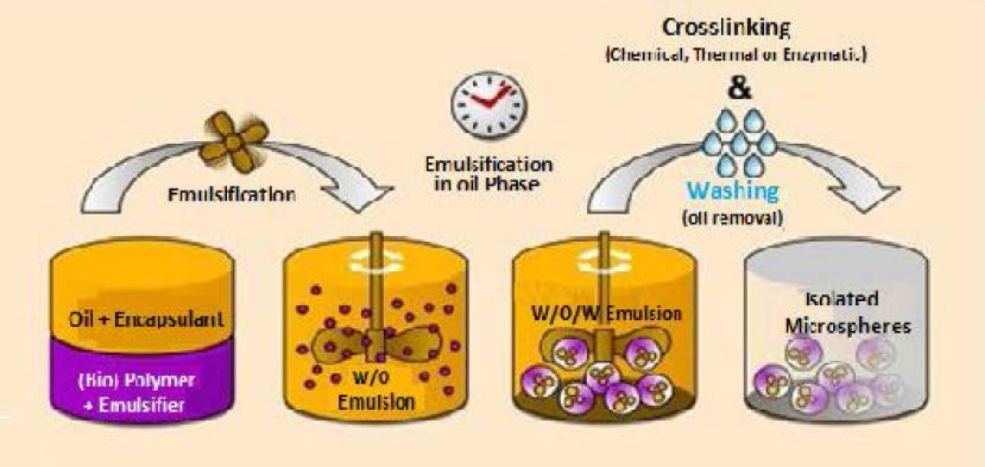

Figure 6: Double emultion technique

Polymerization techniques:

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

Normal polymerization

Interfacial polymerization. Both are carried out in liquid phase.

Normal polymerization:

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymers obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization.

Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

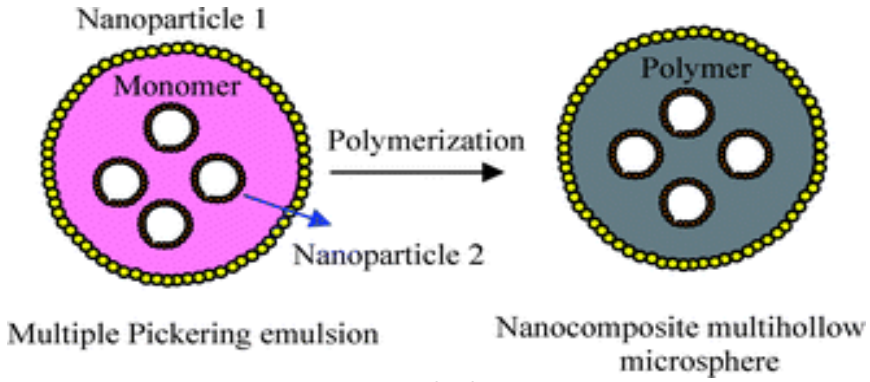

Figure 7: Normal polymerization

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.

4. 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. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very significant since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.

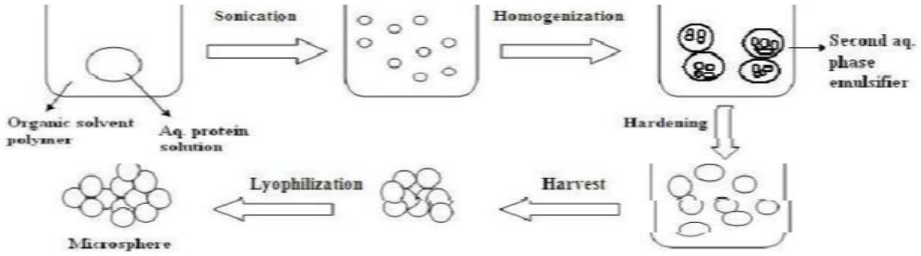

Figure 8: Phase separation Coacervation technique

5. Spray drying and spray congealing:
These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. In this process 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. Microparticles are separated from the hot air by means of the cyclone separator while the
traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillin's. Thiamine mononitrate and sulpha ethylthiadizole15 are encapsulated in a mixture of mono- and diglycerides of stearic acid Palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles

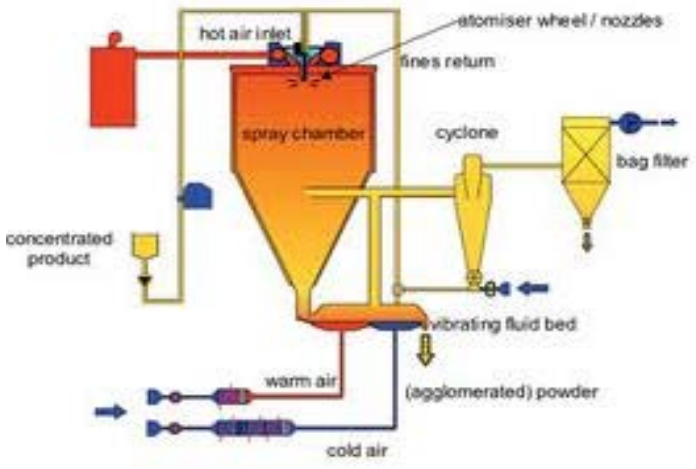

Figure 9: Spray drying method

Solvent extraction method:

Solvent evaporation method is used for the preparation of microparticles, involves removal of the**,** organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer**.**

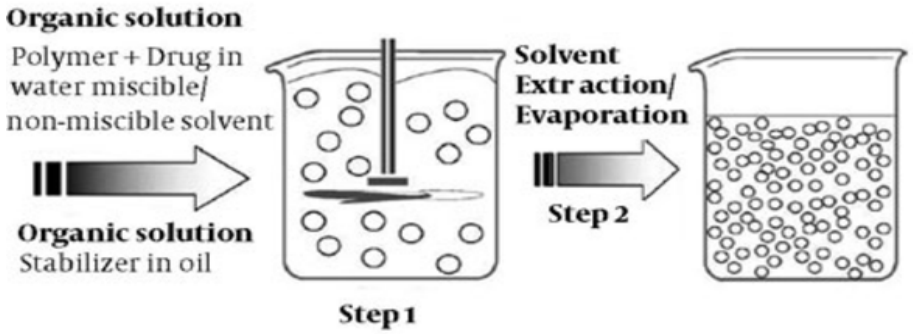

Figure 10: Solvent extraction method

EVALUATION OF MICROSPHERES:

The parameters and methods used to evaluate microspheres are:

Microsphere recovery/yield:

These studies involve determination of the amount of microsphere obtained at the end of preparation and polymer and drug that are consumed in its preparation. It can be calculated by the formula.

Percentage Yield = Practical yield x 100/Theoretical yield

Practical yield of microspheres = Amount of encapsulated drug/ Amount of added drug

Drug Entrapment Efficiency:

It is determined by calculating the amount of drug that is entrapped in the microsphere and the drug which is adsorbed on the surface or interior of the polymer. The amount of free, adsorbed and entrapped drug should be capable of being determined separately and this determination indicated the efficacy of the microsphere produced in terms of its active ingredients.

Determination of free drug in microspheres (unentrapped drug):

Accurately weighed microsphere is taken in a beaker. Saline is added to the mixture and shaken well to liberate the free drug present in the polymeric matrix. The free drug is quantified by suitable analytical method.

It is calculated by:

Percentage loading of microsphere = Quantity of free drug present/Weight of microsphere

The amount of drug present at the surface is measured by digesting the microsphere with saline (0.9%w/v) at room temperature, sonicating the solution in an ultrasonic bath for 5 min and centrifuging it at 3000vpm for 2 min. The supernatant is filtered through 0.45µm filter and the drug is quantified by a suitable analytical method.

Percentage loading of microsphere = Quantity of drug present/Weight of the microsphere

Entrapped drug in micro sphere:

The residue left over from the extraction of the free and adsorbed drug is mixed with 5ml of 0.1m glacial acetic acid. The sample is centrifuged at 5000rpm for 10 minutes. The supernatant is filtered through 0.45µm filter and the amount of drug entrapped is quantified by suitable analytical method.

Percentage of the encapsulated drug =Quantity of drug encapsulated (g)/Quantity of drug added for encapsulation

Surface Morphology:

It provides vital information about the porosity and microstructure of these drug delivery systems. The most common technique used is scanning electron microscopy (SEM).The sample prepared for this method should be dehydrated as vacuum field is necessary for image generation in SEM (shown in figure:16). Prior to loading the samples are coated with electron dense coating materials such as gold, palladium or a combination of both to take photomicrograph. The coating can be done by sputter coating or thermal vacuum evaporation.

Particle Size Analysis:

Particle size characterization is an important study of ensure that the particle size of the formulation lies in the optimal range. A wide variety of methods which employ different physical principles for the determination of size include:

(A) Manual:

a) Optical Microscopy

b) Electron Microscopy

(i) Transmission electron microscopy
(ii) Scanning electron microscopy
c) Sieving
d) Sedimentation (Andreason Pipette Method)
(B) Automated:
a) Particle counters
(i) Optical particle counting
(ii) The counter principle
(iii) Permeability
(iv) Impaction & inertial techniques
b) Light Scattering
(i) Dynamic light scattering
(ii) Enhance laser diffraction
c) Flow cytometry
d) Field flow fractionation

In vitro Release Studies:

These studies aid in understanding the behavior of these system in terms of drug release and their efficacy. Since microsphere is heterogeneous system, the drug release form the polymer taken place through a diffusion process, in an in vitro environment. As a result, the drug and polymer matrix form a biphasic system by separating the phases. Hence the release of the drug is determined by the extent of degradation of polymeric microsphere. The in vitro release experiment can be performed using the dialysis method. In this method, a weighed quantity of the microsphere is placed in a dialysis bag, which is immersed in a larger volume of continuous phase acceptor fluid. The compartment is stirred and the drug which different uses out of the microspheres into the continuous phase is periodically sampled and assayed *in-vitro* studies by incubating micropartides in PBS alone and PBS in a dialysis tube, in internal and gastric media.

Differential Scanning Calorimetric (DSC) Analysis:

The DSC technique can provide information about physicochemical status of the drug in the microsphere. This involves an endothermic or exothermic process and the related thermal transitions include melting, recrystallisation and decomposition, out gassing or a change in the heat capacity of the listed material. DSC is used to monitor different samples of the same materials to assess their similarities/differences, or the effects of additives on the thermal properties of the material.

In-vivo Tissue Distribution Studies:

In vivo studies are a key component of any study since they provide tangible evidence of the efficacy of microspheres, and because the properties exhibited by microsphere are crucial for understanding the functional characteristics of formulation in a biological system. To examine the appropriate properties of the formulation in vivo, adult albino mice/wirstar rats/ Rabbits, etc of certain specified weight can be used. A calculated dose of the drug is administered to each animal as dispersion in saline with 1% of tween 80. At predetermined time intervals, the animals are injected with the microsphere through the tail route vein and sacrificed by cervical dislocation. The organs like lungs, liver, kidneys, heart and spleen are extracted and studied for target action. The tissue samples are stored for 24 hrs at - 200c. Then the concentration of drug localized in each organ is determined quantitatively using the HPLC method.

In vivo tissue distribution studies in animal

Models are carried out to prove the hypothesis of targeting of microsphere/formulation to the organs and compare them with conventional dosage forms of the drug

Advantages of floating drug delivery system:

These advantages include:

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS are advantageous for drugs meant for local action in the stomach e.g. Antacids
3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
5. The FDDS are advantageous for drugs absorbed through the stomach e.g. ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
6. Controlled delivery of drugs. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
7. Treatment of gastrointestinal disorders such as gastro esophageal reflux.
8. Ease of administration and better patient compliance.
9. Site-specific drug delivery.

Disadvantages of floating drug delivery systems:

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
3. Floating systems is that they need a sufficiently high level of fluids in the stomach, so that the drug dosages form float in stomach and work efficiently.

4. These systems also require the presence of food to delay their gastric emptying.
5. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
6. Drugs that cause irritation and lesion to gastric Mucosa are not suitable to b e formulated as floating drug delivery systems.
7. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Applications:

Medical application:

➢Release of proteins, hormones and peptides over extended period of time.

➢Gene therapy with DNA plasmids and also delivery of insulin.

➢Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.

➢Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial/ intravenous application.

➢Tumour targeting with doxorubicin and also treatments of leishmaniasis.

➢Magnetic microspheres can be used for stem cell extraction and bone marrow purging.

➢Used in isolation of antibodies, cell separation. And toxin extraction by affinity chromatography.

➢Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.

Radioactive microsphere's application:

➢ Can be used for radio embolisation of liver and spleen tumors.

➢ Used for radio synvectomy of arthritis joint

➢ Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done.

Other applications:

➢ Fluorescent microspheres can be used for membrane based technologies for flow cytometry, cell biology microbiology.

➢ Yttrium 90 can be used for primary treatment of hepato cellular carcinoma and also used for pre transplant management of HCC with promising result.

Dosage form	Drug	Polymers	Methods
Multiparticulate FDDS	Zolpidem Tartarate	Eudragit	Gas generation technique
Floating microspheres	Cephalexin	Ethyl Cellulose (EC)	Emulsion solvent evaporation
Hollow microspheres	Ranitidine HCl	Eudragit	Solvent evaporation method
Floating microparticles	Metoprolol succinate	Polymethacrylates Eudragit S100	Non-aqueous emulsion solvent evaporation method
Floating microspheres	Aceclofenac	Eudragit S 100 (ES) :Eudragit RL 100	Emulsion solvent diffusion technique
floating tablets			Gas generation technique

Table 2: Marketed products of FDDS

New approaches in gastro retentive drug delivery system with their merits and demerits:

High density system Sinking systems:

That retained at the bottom of the stomach. In this system density of pellets/tablets greater than density of stomach fluid.

Merits:

These systems with a density of about 3 g/cm3 retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements and allow the release of drug for a prolonged period of time

Demerits:

Difficult to manufacture such formulations with high amount of drug (>50%)

Technically also difficult to achieve a density of about 2.8 g/cm3

Effectiveness of this system in human beings was not observed and thus such

System has not been marketed.

Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.

Low density system:

In this system density of pellets/tablets less than density of stomach fluid.

Merits:

- Improves better patient compliance.
- No risk of dose dumping.
- Increases the bioavailability of a drug.
- Reduce the frequency of dosing.

•In this system dosage forms floats on gastric fluid and releases the drug slowly for a longer period of time.
• The HBS are advantageous for drugs that are absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
• This approach is most widely used.
• Single unit low density system is associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation.
• Single unit low density system is unreliable in prolonging gastric residence time in the stomach when administered orally.

Demerits:

• One drawback of hydrodynamically balanced systems is that this system, being a matrix
Formulation consists of a blend of drug and low-density polymers. The release kinetics of
The drug cannot be changed without changing the floating properties of the dosage form and Vice-versa.
• Floating drug delivery systems require high fluid level in stomach to float and work
Effectively.

Swelling system:

These are the dosage forms, which after swallowing, swell to an extent that prevents their Exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time.

Merits:

• Improves better patient compliance.
• No risk of dose dumping.
• Increases the bioavailability of the drug.
• Reduce the frequency of dosing.
• Allow the release of drug for a prolonged period of time.
• Swelling of the dosage form causes floating of the dosage form and thus the system requires high fluid level in the stomach for the floating of the dosage form and to work effectively.
• The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.

Bioadhesive system:

These systems are used to localize a delivery device within the lumen and cavity of the body to increase the drug absorption process in a site-specific manner.

Merits:

• Improves patient compliance.
• No risk of dose dumping.
• Increases the bioavailability of the drug.
• Reduce the frequency of dosing.

Demerits:

• Bioadhesion is difficult to maintain due to rapid turnover of mucin in GIT. Expandable system use of size-increasing concept for gastro retention. This system is Capable of increasing in size relative to the initial dimensions.
• Dosage form is small enough to be swallowed, and thus not cause gastric obstruction either singly or by accumulation.
• Increase in size prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach.
• Time consuming.
• Difficulty in formulation.
• Not most widely used.

Magnetic system:

Dosage forms contain a small internal magnet and a magnet is placed in the abdomen over
the position of the stomach that retains the dosage form in the gastric region.

Merits:

• Magnetic system serves as a potential means of extending the gastric retention of the drug in the stomach by increasing duration of contact of system in the gastric region.
• Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only if the external magnet is to be positioned with high degree of precision.
• The external magnet must be positioned with a degree of precision that might compromise patient compliance.

Demerits:

• Not better patient compliance.
• Not most widely use

Ion-exchange resin system:

Coated ion exchange resin beads are loaded with bicarbonate and a negatively charged drug is bound to the resin. Overcome rapid loss of carbon dioxide resultant beads then capsulated in a semi-permeable membrane.

Merits:

• This system floats on the gastric fluid due to exchange of chloride and bicarbonate ions which further causes release of carbon dioxide. Thus the drug was released slowly
for a longer period of time.

Demerits:

• Not most widely used.
• Time consuming.
• Very expensive to formulate this system.

Drug absorption in the gastrointestinal tract is a highly inconsistent phenomenon and prolonging gastric retention of the dosage form extends the time for drug absorption and attempts to make it more consistent as well as reproducible. Floating multiparticulate Drug Delivery

systems promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing towards commercializing this technique. It is hoped that in the near future bio pharmaceutically better Therapeutic systems in the form of floating drug delivery devices would be introduced in clinics in greater number

Conclusion:

It has been observed that microspheres are better choice of drugs delivery system. Because of it is having advantage of target specificity and better patient compliance. Its applications are more they are used for the many disease treatment's in future microspheres will have an important role to play in the advancement of medical field.

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