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A Review on: Floating Microsphere

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ABSTRACT

Microspheres are free flowing particles ranging from 1-1000u. Microspheres are having wide applications in drug delivery system. They are mainly used for targeted drug delivery of anti-cancer agents, ophthalmic agent and can be used for diagnosis purpose. In this article detail discussion was made on the polymers, preparation methods and applications of microspheres in pharmaceutical dosage form development. General methods of preparation are emulsion techniques, phase separation coacervation techniques, spray drying and spray congealing and solvent extraction, in-situ polymerization etc. Advantages of microspheres use are targeted drug delivery, optimal therapeutic effects and minimum side effects. Recent trends are floating microspheres, radio immobilization using microspheres. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Keywords: Microspheres, Characterization, Mechanism of release, Evaluation, Challenges Drug Delivery, Floating drug delivery systems, Gastro-retentive floating microspheres, Gastric retention.

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INTRODUCTION[1-8]

The primary aim of oral controlled drug delivery is the most preferable route of drug delivery system is to achieve better bioavailability and release of drug from the system which should be predictable and reproducible, easy for administration, patient compliances and flexibility in formulation for effective therapy or to improve therapeutic efficiency of the drug through improved bioavailability Gastro retentive dosage forms significantly extend for the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance. Gastric retention can be achieved by the mechanism of mucoadhesive or bio adhesion systems, expansion system, high density systems, magnetic systems, super porous hydrogels, raft forming systems, low density system and floating ion exchange resins. Floating drug delivery systems or hydro dynamically balance systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. The drug is released slowly at a desired rate from the system and drug residual systems are emptied from the stomach. This results in increase in the gastric residence time and a better control of qualification in plasma drug concentration. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as micro particles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on type of material and size of the material. 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. 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.

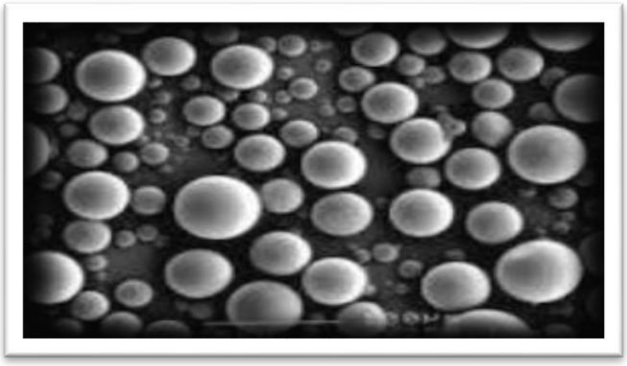

Figure 1: Microspheres.

Two most common types of polymer [9-10]

- Polyethylene microspheres
- Polystyrene microspheres

Polyethylene microspheres:

Polyethylene microspheres are commonly used as permanent or temporary filler. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. High sphericity of polyethylene microspheres, as well as availability of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences, process troubleshooting and numerous research applications. Charged polyethylene microspheres are also used in electronic paper digital displays.

Polystyrene microspheres:

Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immune precipitation. Proteins and ligands adsorb onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments.

APPROACHES TO GASTRIC RETENTION [11-14]

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These includes in figure 2.

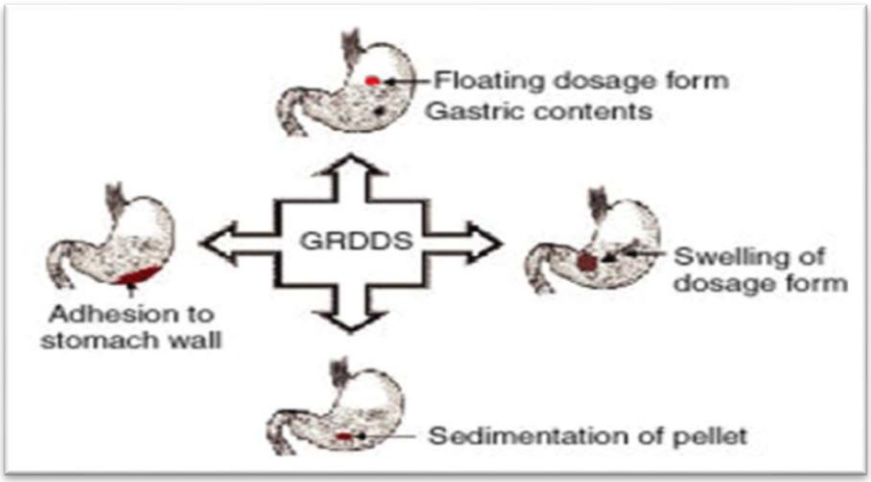

Figure 2: Illustration of types of gastro retentive drug delivery systems [10]

Floating Systems:

Floating systems 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.

Bio/Muco-adhesive Systems:

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending gastric residence time of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. Binding of polymers to mucin/epithelial surface can be divided into three broad categories:

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

Swelling and Expanding Systems:

These are 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 stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit tendency to remain logged at the pyloric sphincter.

High density systems:

These systems with a density of about 3 g/cm3 are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6- 2.8 g/cm3 acts as a threshold value after which such systems can be retained in the lower parts of the stomach. High-density formulations

include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

Incorporation of passage delaying food agents:

Food excipients like fatty acids e.g. salts of meristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

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.

Osmotic regulated systems:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio erodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmetically 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 controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

Advantages of Floating Microspheres [15-18]

- Enhanced bioavailability
- Enhanced first-pass biotransformation
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT
- Reduced fluctuations of drug concentration
- Improved receptor activation selectivity
- Reduced counter-activity of the body
- Extended time over critical (effective) concentration
- Minimized adverse activity at the colon
- Site specific drug delivery
- Less inter- and intra-subject variability.

- Minimizes the counter activity of the body leading to higher drug efficiency.
- Fluctuations in drug concentration are minimized. Therefore, concentration dependent adverse effects can be reduced.
- Sustained mode of drug release enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
- Flexibility in dosage form design.
- Extend patent protection, globalize product, and provide new business opportunities

Disadvantages of Floating Microspheres [19]

- 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.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
- High variability in gastric emptying time due to its all or non-emptying process.
- Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametric size. Therefore patients should not be dosed with floating forms just before going to bed.

Limitations [20]

Some of the disadvantages were found to be as follows:

- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed.

TYPES OF FDDS [21-26]

Based on the mechanism of buoyancy, two distinctly different technologies i.e. no effervescent and effervescent systems have been utilized in the development of FDDS:

- Non-Effervescent FDDS.
- Effervescent FDDS.

Non-Effervescent FDDS

The FDDS belonging to this class are usually prepared from gel-forming or highly swell able cellulose type hydrocolloids, polysaccharide or matrix forming polymers like polyacrylate, polycarbonate, polystyrene, and poly-methacrylate. The drug in the dosage form dissolves in and diffuses out with the diffusing solvent forming a 'receding boundary' within the gel structure. The various types of this system are as:

- Single Layer Floating Tablets
- Bi-layer Floating Tablets
- Alginate Beads
- Hollow Microspheres

Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity.

Bi-layer Floating Tablets:

A bi-layer tablet contains two layers one immediate release layer which releases initial dose from a system while 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.

Alginate Beads:

Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into the aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to the formation of the porous system, which can maintain a floating force for over 12 hours.

Hollow Microspheres:

Hollow microspheres (micro balloons), loaded with a drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The micro balloons floated continuously over the surface of acidic dissolution media containing the surfactant for more than 12 hours in vitro.

Figure 3: Hollow Microspheres

II. Effervescent FDDS

The buoyant delivery system utilized matrices prepared with swellable polymers, such as Methocel or polysaccharides (e.g. chitosan) and effervescent components (e.g. Sodium bicarbonate and citric acid or tartaric acid) or matrices having chambers of liquid that gasifies at body temperature.

These effervescent systems further classified into two types.

1) Gas generating systems
2) Volatile Liquid/Vacuum Containing Systems.

1) Gas – Generating Systems:

- Intra Gastric Single Layer Floating Tablets
- Intra Gastric Bi-layer Floating Tablets

Intra Gastric Single Layer Floating Tablets:

These are formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. 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 fluctuations in plasma drug concentration.

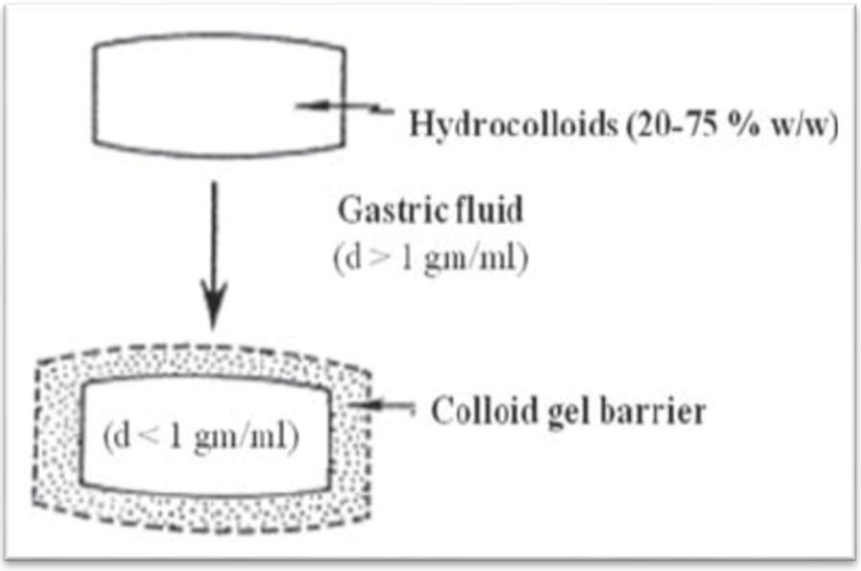

Figure 4: Intra Gastric Single Layer Buoyant Tablet

Intra Gastric Bi-layer Floating Tablets:

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

- Immediate release layer and
- Sustained release layer.

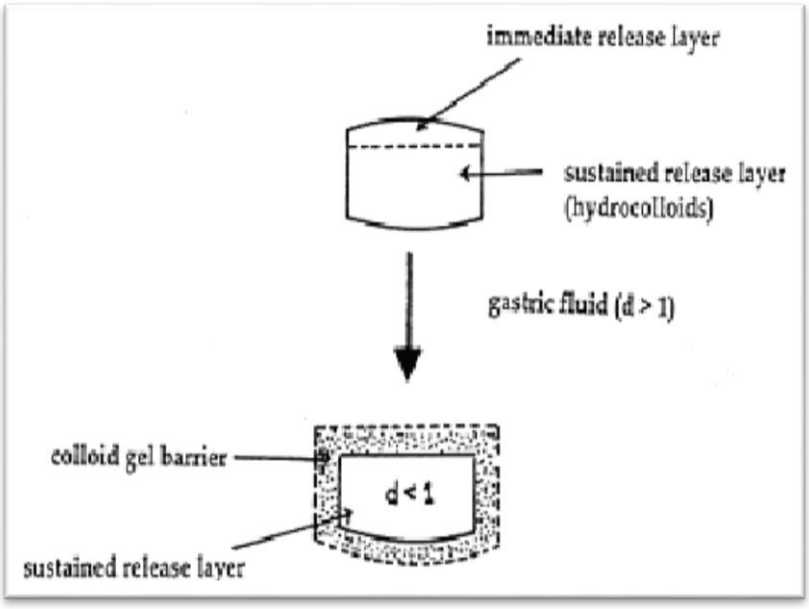

Figure 5: Intra Gastric Bi-layer Buoyant Tablet

Volatile Liquid / Vacuum Containing Systems:

- Intra-gastric Floating Gastrointestinal Drug Delivery System
- Inflatable Gastrointestinal Delivery Systems
- Intra-gastric Osmotically Controlled Drug Delivery System

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.

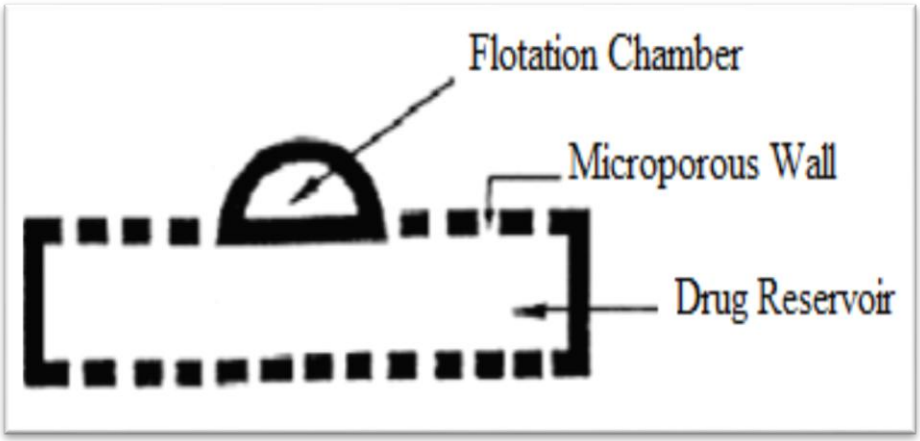

Figure 6: Intra-gastric Floating Gastrointestinal Drug Delivery Device.

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.

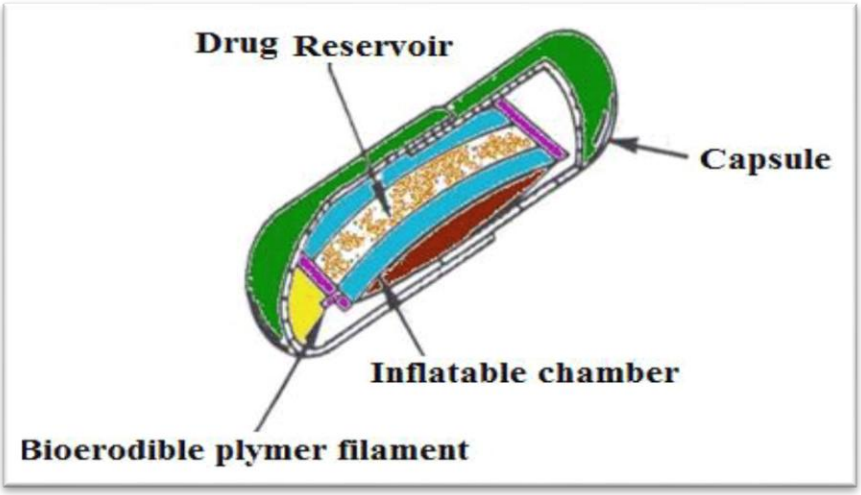

Figure 6: Inflatable Gastrointestinal Delivery Systems

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. 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 vapor 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.

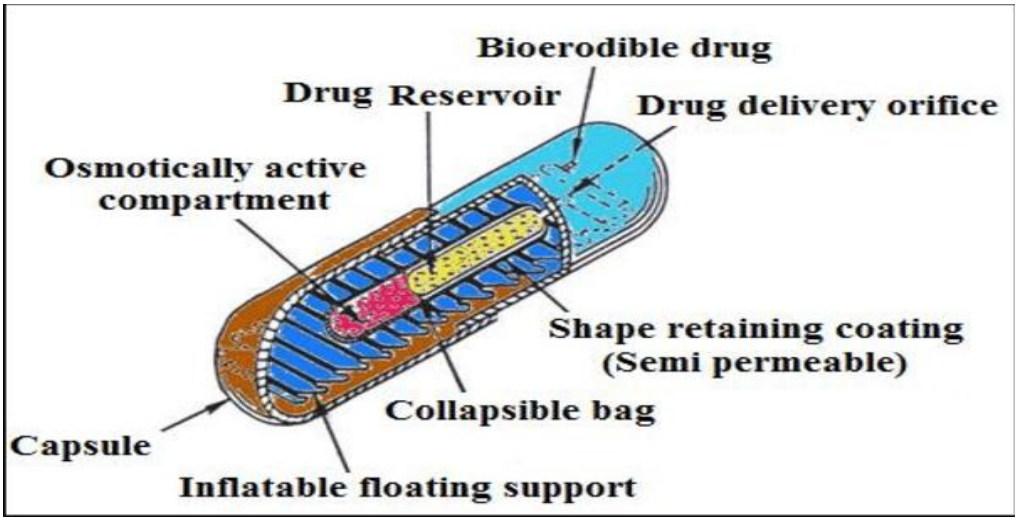

Figure 7: Intra-gastric Osmotically Controlled Drug Delivery System.

MECHANISM OF FLOTATION OF MICROSPHERES [27-29]

When microspheres come in contact with gastric fluid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content is needed to allow proper achievement of buoyancy.

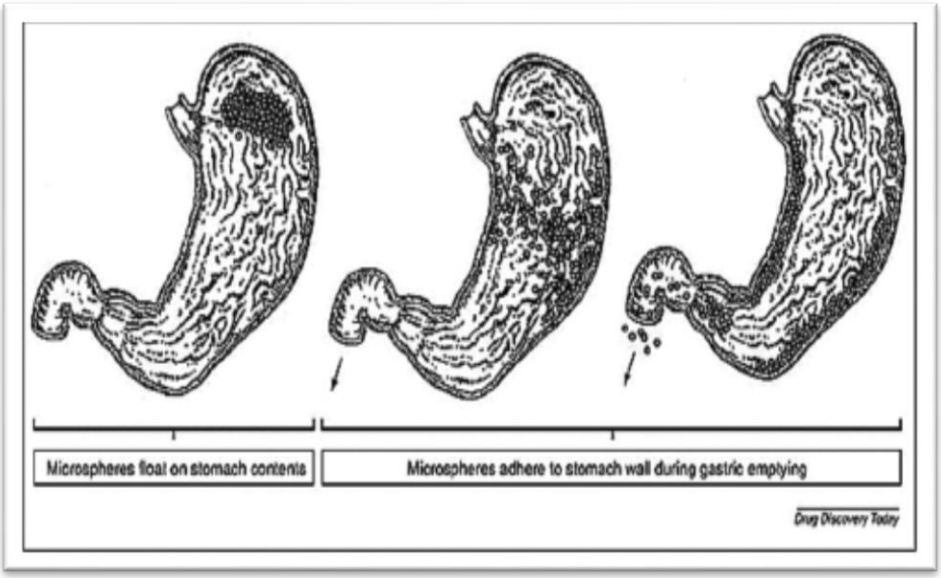

Figure 8: Mechanism of gastro retention of floating microspheres having mucoadhesive polymer

Mechanism of drug release from the microspheres:-

The mechanism of drug release from multi particulates can occur in the following ways: - Diffusion On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior. Erosion some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. Osmosis In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

METHOD OF PREPARATION OF FLOATING MICROSPHERES [30-46]

1) Single emulsion techniques.
2) Double emulsion techniques.
3) Polymerization.

a) Normal polymerization -Bulk -Suspension –Emulsion.

b) Inter-facial polymerization.

4) Phase separation coacervation technique.

5) Spray drying.

6) Solvent extraction.

7) Wax coating Hot-melt method.

Single emulsion technique:

There are several Proteins and carbohydrates, which are prepared by this technique. In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e. non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods.

- **Cross linking by heat:**

By adding the dispersion into heated oil, but it is unsuitable for the Thermo labile drugs.

- **Chemical cross linking agents:**

By using agents i.e. formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) by adding to Liquid paraffin containing a surfactant resulting formation of w/o emulsion. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent.

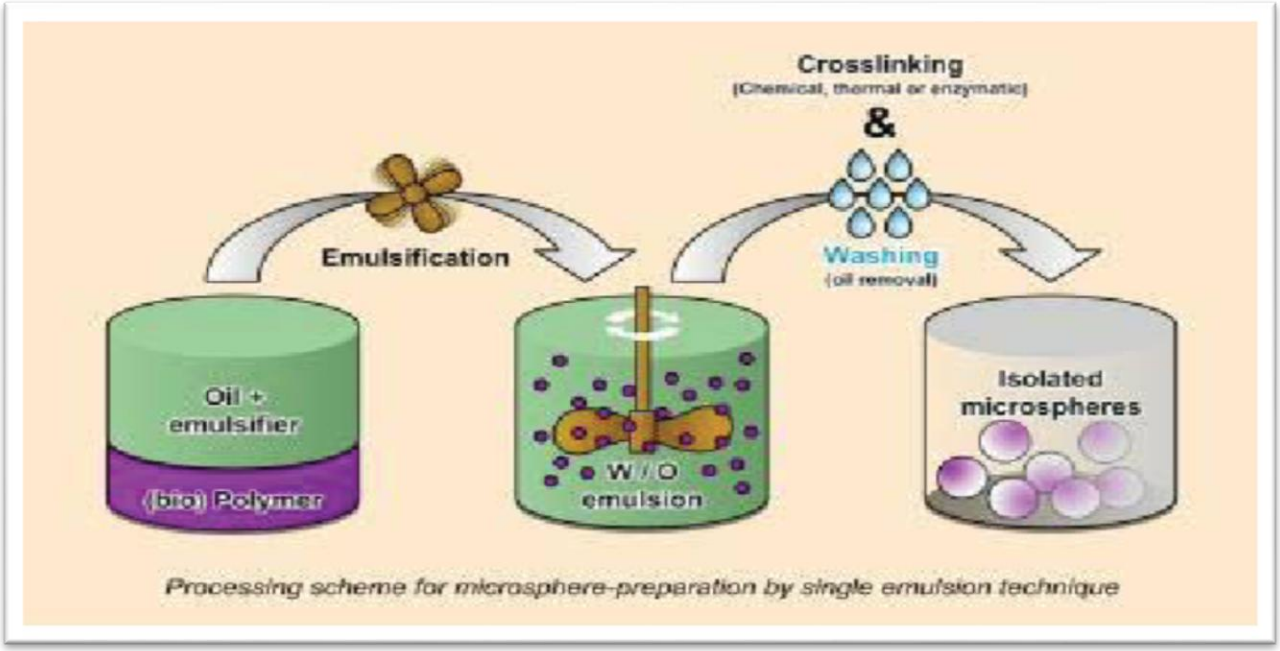

Figure 9: Microspheres by Single Emulsion Technique

Double emulsion technique:

It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put a t constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e. formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e. multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and drying and collection of microspheres genistein chitosan microsphere were prepared by the o/w/o multiple emulsion method.

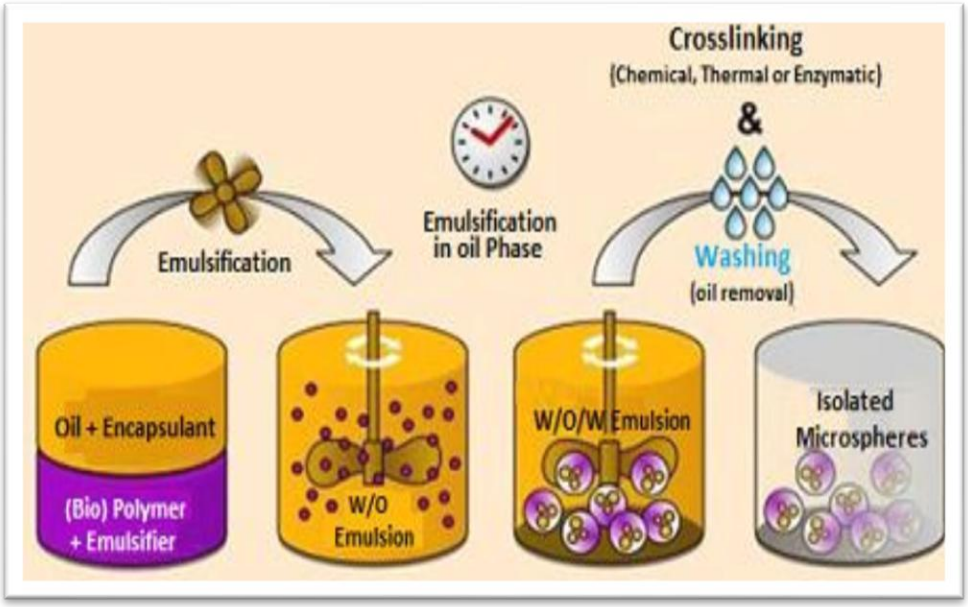

Figure 10: Microspheres by Double Emulsion Technique

Polymerization techniques:

Mainly two techniques are using for the preparation of microsphere are classified as.

Normal polymerization:

In bulk polymerization, a monomer or a mixture of number of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done by adding the drug during the process of polymerization. It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermo labile active ingredients. Suspension polymerization is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with

active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less the 100 µm. Emulsion polymerization is differ from the suspension as due presence of initiator in aqueous phase but is also carried out at low temperature as suspension external phase normally water in last two techniques so through which heat can easily dissipate .formation of higher polymer at faster rate is possible by these techniques but association of polymer with the un reacted monomer and other additives can occur.

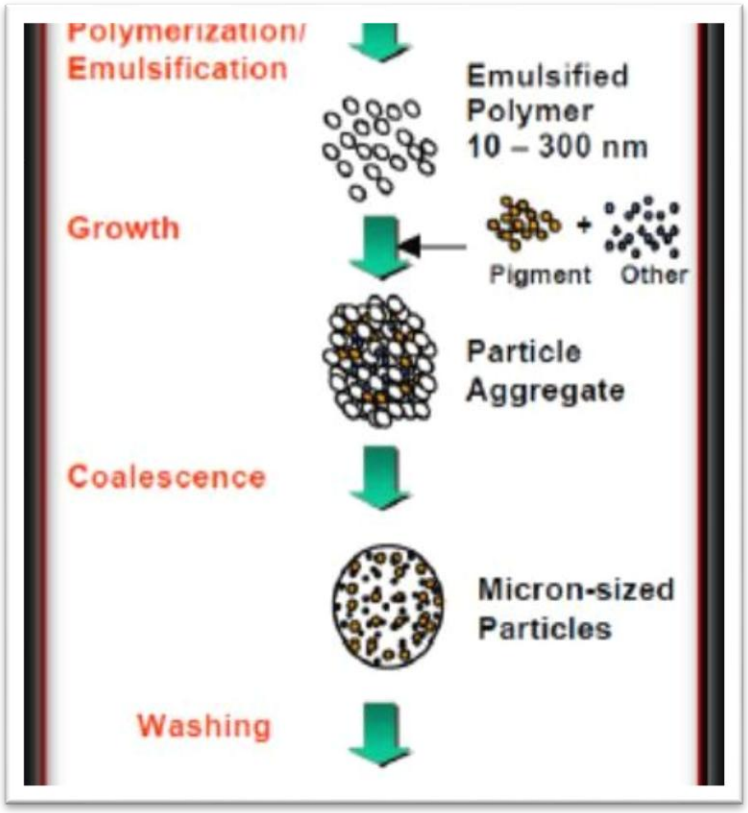

Figure 11: Microspheres by Polymerization techniques

(b) 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. In this technique two reacting monomers are employed; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet.

Phase separation coacervation technique:

It is the simple separation of a macromolecular solution into two immiscible liquid phases. In this process, the polymer is solubilized to for a solution. This process is designed for preparing the reservoir type system e.g. encapsulate water soluble drugs i.e. peptides, proteins etc1. The principle of coacervation is decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, formation of dispersion of drug particles 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. Matrix types preparations can also be prepared by this process for hydrophilic drug e.g. steroids, 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.

Spray drying and spray congealing:

Concept of spray drying technique (fig 9) depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray is congealing. Evaporation is the basic mechanism in spray drying, whereas in spray congealing it is that of a phase inversion from a liquid to a solid. Both processes are similar, except for energy flow. Spray drying is the most widely used industrial process involving particle formation and drying. Therefore, spray drying is an ideal process where the end product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape

Principle:

Three steps involved in spray drying:

Atomization: of a liquid feed change into fine droplets.

Mixing: it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

Dry: Dried powder is separated from the gas stream and collected. In this technique 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, this form small droplets or the fine mist, from which the solvent evaporates instantaneously leading the formation of the microspheres. The size range is 1-100 μm. By using hot air separate of Micro particle by means of the cyclone separator while the traces of solvent are removed by vacuum drying. Advantages of the process are feasibility of operation. This technique is very useful to encapsulate various penicillin's. Thiamine mononitrate10 and sulpha ethylthiadizole11 are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however

leads to the formation of porous micro particles. The sprays are produces by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. The microsphere size is controlled by the rate of spraying, nozzle size, temperature (in drying and collecting chambers.) and the feed rate of polymer drug solution. The quality of product is improved by addition plasticizer spray flow rate should kept constant around 6ml/min. Spray drying technique is also useful for preparing chitosan microsphere In Used formaldehyde as a crosslinking and also reported a novel method in which cimetidine and famotidine were entrapped in microspheres prepared by spray drying of multiple emulsion (o/w/o or w/o/w). They found that the release of the drugs from microspheres by this novel method was significantly sustained as compared to those prepared by conventional spray drying or o/w emulsion method. Was used spray drying used for the preparation of PCL microspheres of ketoprofen. (c2) He used the organic solution of the drug and two polymers, cellulose acetate butyrate and PCL was made in a mixture of dichloromethane and chloroform (1:1). The prepared solution was sprayed through a nozzle in a spray-drier under different experimental conditions. Solid microspheres were collected into final bottom vessel spray-drier.

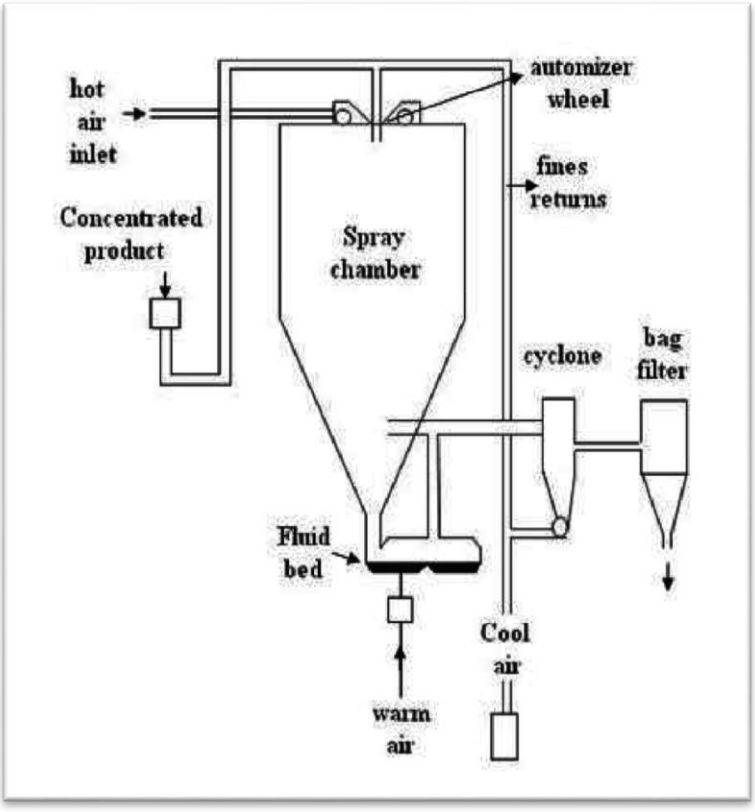

Figure 12: Spray drying method for preparation of microspheres.

Advantages and Disadvantages:

Spray drying is very useful for pulmonary drug delivery as well as for oral dosages form and it is remarkable versatility of the technology, and a wide range of product can be obtained by this technique. It is very flexible and reproducible method that, why number of industries use this technique for drying operation. It can be designed to virtually any capacity required easily. Can be used with both heat-resistant and heat sensitive products. Powder quality remains constant during the dryer. Particles which produced uniform in size and frequently hollow thus reduce the bulk density of the product. But there are some drawbacks in technique; the equipment is very bulky and expensive. The overall thermal efficiency is low, as the large volumes of heated air pass through the chamber without contacting a particle.

Solvent extraction:

In this method preparation of micro particles, involves removal of the organic phase by extraction of the organic solvent. Isopropanol can be used as water miscible organic solvents. By extraction with water, Organic phase is removed. Hardening time of microsphere can be decrease by this method. 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.

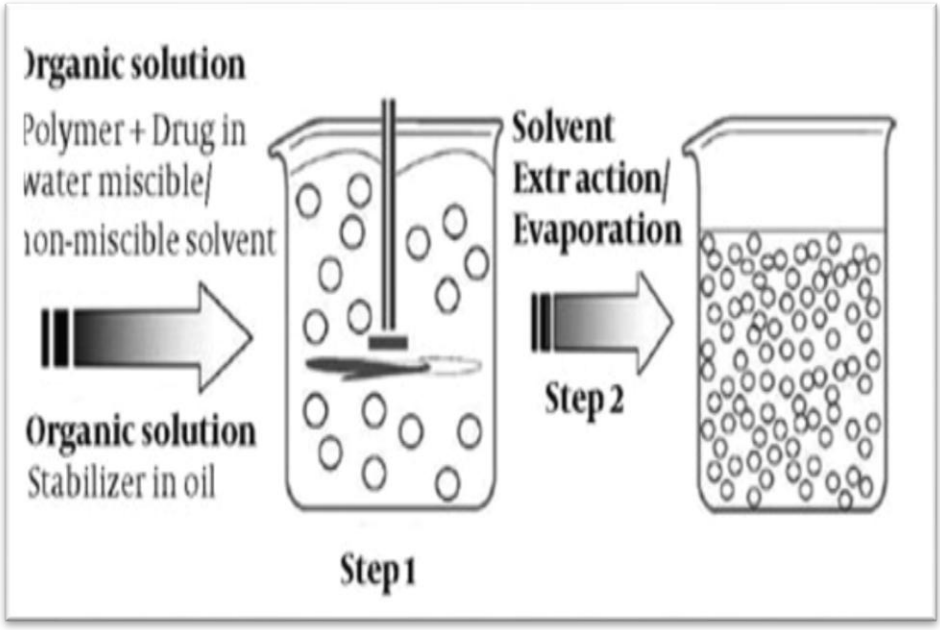

Figure 13: Microsphere preparation by solvent extraction

Wax Coating and Hot Melt In this technique:

Polymer is dispersing in suitable dispersion medium and slowly cooled to form the microspheres. The polymers which having low melting point fabricated into microspheres by this technique easily. For coating and coring of particle wax is use mostly. In which encapsulate the drug by dispersion in

the molted wax. The wax suspension is dispersed by high speed mixing into cold solution for example liquid paraffin. Agitate the mixture for one hour. Then decanted the external phase and suspended microspheres collect from solvent. And allow drying it in air. It is inexpensive method as comparison to others and drug release is more rapid. Mostly Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics.

APPLICATIONS OF FLOTING MICROSPHERES [47-62]

Applications are explained as follows:

(A) Magnetic microspheres:-

These microspheres are used for delivering the drug at localized disease site. Magnetic drug Delivery by particulate carriers is used for this very purpose. In magnetic targeting, a drug or Therapeutic radioisotope is bound to a magnetic compound, injected into a patient's blood stream, and then stopped in the target area with a powerful magnetic field.

(B) Radioactive microspheres:-

Therapeutic radioactive microspheres (radio labeled microspheres) are appropriate for therapy when the encapsulated diagnostic radioisotope has been exchanged for a therapeutic one from the α- or β-emitter group. Typical uses include local application for the treatment of rheumatoid arthritis, liver tumors and cystic brain tumor. However, their use remains experimental because of unwanted toxicity, smaller than expected target uptake and insufficient treatment effects that have resulted from radio chemical instability and suboptimal bio-distribution of the radiopharmaceutical moiety. In spite of proven superior results of many radiation therapies there exists a general negative attitude towards the use of radioactive substances few therapeutic applications of radioactive microspheres are tabulated in Table: 1

Table: 1 Therapeutic application of microspheres

Type of radioactive microspheres	Applications
90Y-glass microspheres, 186Re/188Re-glass Microspheres	Radio immobilization of liver and spleen Tumors
35S-colloid, 90Y-resin microspheres, 169Er.citrate	Radio synovectomy of arthritis joints 90Y labeled poly (lactic acid) microspheres, 211At-microspheres
212Pb-sulfur colloid	Local radiotherapy
Chromium 32P-phosphate, 90Y-silicate	Intra cavity treatment

Table: 2 Diagnostic applications of radioactive microspheres

Type of radioactive microspheres	Applications
111In or 51Cr-labelled red blood cells	Gated blood pool study
111In-labeled platelets 99mTc-sulfur colloid	Thrombus imaging in deep vein thrombosis Polystyrene

	microspheres labelled with γ-Emitters
141Ce, 57Co, 114mIn, 85Sr, 51Cr	Blood flow measurements
3H, 14C-labelled microspheres 141Ce polystyrene microspheres	Investigation of bio distribution and fate of drug loaded microspheres
99mTc-impregnated carbon particles 99mTc macro aggregated human serum albumin	Lung scintigraphy
99mTc-macro aggregated human serum albumin	Radio immobilization
99mTc-macro aggregated human serum Albumin	Liver and spleen imaging
99mTc-sulfur colloid 99mTc-antimony sulphide colloid	Bone marrow imaging

(C) Perfect count microspheres:-

These microspheres are meant for in vitro diagnostic use. These microspheres are meant for determination of absolute counts of cells in peripheral blood, bone marrow, leukophoresis and culture medium samples using flow cytometry. These are micro-bead-based single platform system, which can be used in combination with monoclonal antibodies conjugated with different flurochromes for absolute counts, which helps to identify the cell subpopulations for which the absolute count is intended.

(E) Microsphere sensors:-

Optical microspheres are proving to be best candidates for label-free biochemical sensors. Light of resonant frequencies circulates on the surface of the microsphere in the form of Whispering-gallery modes (WGMs). High-Q factor of microspheres allow the interaction Between the WGM and the surrounding medium. The WGM's resonant wavelength is extremely sensitive to slight changes in refractive index near the sphere's surface when Molecules bind to or are removed from the surface. Microsphere sensors are used for heavy Metal detection, detection of protein and DNA molecules and refractometric sensing. Microsphere sensors have also been used for small molecule detection. Detection of small Molecules is challenging because the transduction signal in label free sensors is generally proportional to the mass of the target molecule.

(G) Fluorescent microspheres:-

These are made of polystyrene or poly vinyl toluene, mono disperse system. Their size ranges from 20nm to 4µm. Preparation of fluorescent microspheres involves swelling the polymeric microsphere followed by incorporation of fluorescent dyes in the microspheres pores. The main applications for Estapor® Fluorescent Microspheres (commercial fluorescent microspheres) are the following: Membrane-based technologies Flow Cytometry, Embolization, Confocal Microscopy FLISA

(Fluorescent Linked Immunosorbent Assay), and Toxicology, Cell Biology, Microbiology, Biosensors, Biochips and Micro fluidics.

(H) Microspheres in molecular biology:-

During the study of the underlying genetic causes of disease a need for multiplexed analytical genotyping methods have been increased. Although microarray platforms have attempted to fulfill this need, their acceptance in the clinical diagnostic setting has been limited. Microspheres have been used for the detection of six single nucleotide polymorphisms (SNPs) believed to be associated with venous thromboembolism, a classic example of a complex, multifactorial disorder involving multiple genetic abnormalities Pyro sequencing is real-time DNA sequencing by synthesis. Pyro sequencing currently has many applications, including determination of single nucleotide polymorphisms, resequencing of PCR products, microbial typing, and analysis of secondary DNA structures such as hairpins. The pyro sequencing technique utilizes DNA templates which are attached to magnetic microspheres, which can easily be put on an electro wetting chip in solution. On a digital micro fluidic platform, pyro sequencing could be accomplished by merging droplet containing the magnetic microspheres with the wash droplets and then resolving the double volume droplet through droplet splitting.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS [19]

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the GIT. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

Sustained Drug Delivery:-

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents.

Site-Specific Drug Delivery Systems:-

The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug.

Absorption Enhancement:-

Drugs which are having poor bioavailability because of site-specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

Reduced Fluctuations in Drug Concentration:-

Continuous input of the drug following Controlled release Gastro-retentive dosage form (CRGRDF) administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration-dependent adverse effects that are associated with peak concentrations can be prevented.

Table 3: Types of Dosage Form

Sr. No.	Dosage form	Drugs
1	Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
2	Granules	Diclofenac sodium, Indomethacin, Prednisolone
3	Films	Cinnarizine
4	Powders	Several basic drugs
5	Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-Dopa, Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid.
6	Tablets/pills	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnarizine, Diltiazem, Fluorouracil,

EVALUATION OF FLOATING MICROSPHERES [63]

Particle size:-

The particle size of the microspheres was measured using an optical microscopic method and mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micro meter.

Bulk density:-

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10 gm. sample of granules was placed into 25 ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and the bulk density was calculated using the equation **(values expressed in gm. /cm3)**

Bulk Density = Weight of Sample / Volume of Sample

Tapped density:-

The tapping method can be used to calculate tapped densities. The volume of weighed quantity of microspheres was determined after 100 taps as well as 1000 taps using tapped density apparatus.

Tapped Density = Weight of Sample /Tapped Volume

Compressibility Index and Hausner Ratio:-

Compressibility index and hausner ratio was calculated from the values of bulk density and tapped density by using following formulas:

% Compressibility Index = tapped density – bulk density / Tapped density x 100

Hausner Ratio = Tapped Density / Bulk Density.

Angle of Repose:-

The angle of repose θ of the microspheres, which measures the resistance to particle flow, was calculated as…….

$$\mathbf{Tan\ \theta = h/r}$$

Therefore = tan-1 h/r

Where,

θ is angle of repose.

h is height of the pile.

r is the radius of the pile.

Table 4: Carr's Index as an Indication of Powder Flow

Carr's Index	Types of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very Poor
>40	Extremely Poor.

Table 5: Relationship between angle of repose (θ) and flow ability

Angle of Repose	Flow ability
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

Percentage yield:-

Percentage yield of floating microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula.

% yield = (Actual weight of product/Total weight of drug and Excipients) ×10

Drug entrapment efficiency (DEE):-

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 is measured by spectrophotometer 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

Swelling studies:-

Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies may be determined by using dissolution apparatus, optical microscopy and other sophisticated techniques which include H1 NMR imaging, confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus was calculated as per the following formula.

Swelling Ratio = Weight of wet formulations /Weight

Scanning Electron Microscopy (SEM):-

Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure.

In-vitro buoyancy:-

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

Buoyancy (%) = Wf/ Wf+Ws x 100

Where, Wf and **Ws** are the weight of floating and settled microsphere respectively.

In-vitro drug release studies:-

For such type of studies USP dissolution apparatus at particular speed is used. Distilled water and dissolution fluid is maintained at 37±10C. Samples withdrawn at periodical intervals and are analyzed spectrophotometric ally. The volume was replenished with the same amount of fresh medium to maintain the sink condition.

CONCLUSION

Microsphere offer vast advances in the pharmaceutical field. The recent use allows targeting the delivery of such drugs which offers difficulties in their normal delivery. Now higher dose can be administered as microspheres thus limiting gastrointestinal side-effects and allowing a full course of antibiotics to be given in a single dose. In recent years, studies of microspheres have been increased so that it may be used in more diverse applications and it is evident that the range of its applications is vast and enormous. For biologists, microspheres have emerged as an exciting new platform in the

investigation of cellular processes and bimolecular interactions. The future certainly looks bright for microspheres, particularly in the areas of proteomics, genomics and drug discovery.

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