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**Review Article.....!!!**

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## **FLOATING MICROSPHERE FOR GASTRO RETENTIVE DRUG DELIVERY- A NOVEL APPROACH**

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and Evaluations

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### **ABSTRACT**

Floating drug delivery systems are designed for the poorly soluble, unstable and locally acting drugs. Floating drugs are having low density property than the gastric content which enables them to float in the stomach fluid for a prolonged period. This novel approach inspires to design a floating microspheres is one of the approach in delivering a dosage form to the target site in sustained controlled release fashion, to achieve good peak plasma concentration by increasing bioavailability of drug or dosage form. Comparing to the conventional dosage form floating microspheres have improved G.I.T absorption, controlled release, site specificity and have potential to improve local action with maximum gastric retention time and predictable gastric emptying time. microspheresthe release of the drug at specific site with specific rate. These systems have several advantages over conventional multi dose therapy. One such approach is using microspheres as carriers for drugs. Microspheres efficiently utilized in controlled delivery of many drugs but wastage of drug due to low drug entrapment efficiency is the major drawback of such micro-particulate system. This review provides a brief information about types of microspheres, method of preparations, evaluation and application of microspheres for controlled drug delivery.

## INTRODUCTION

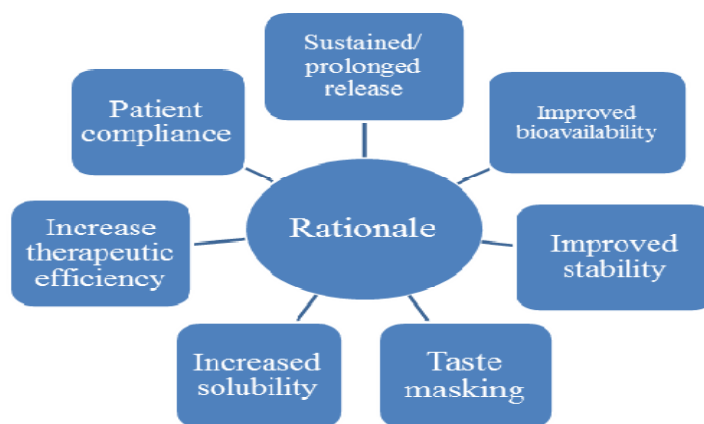
Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Conventional drug delivery system maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption pioneered the idea of development of Gastroretentive drug delivery system (GRDDS<sup>1</sup>). On the basis of the mechanism of mucoadhesion, floatation, sedimentation or by the simultaneous administration of pharmacological agents, the controlled gastric retention of solid dosage forms may be achieved, which delay gastric emptying. The single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly which results in more reproducible drug absorption and reduced risk of local irritation. Controlled release drug delivery systems that can be retained in the stomach for a long time have many advantages over sustained release formulations. Such retention systems are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. If the drugs are poorly soluble in intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in improved bioavailability. Such systems are advantages in improving gastrointestinal absorption of a drug with narrow absorption windows as well as for controlling release of a drug having site-specific absorption limitations. Such systems are useful in case of absorption of albuterol where drug is best absorbed in stomach. Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time, thereby resulting in improved bioavailability for some drugs. For levodopa, gastric emptying controls its delivery at the site of action, which is

proximal small intestine. In this case it will be useful if gastric emptying can be controlled to achieve maximum effect of the drug<sup>6</sup>. B-lactam antibiotics when administered in conventional forms are absorbed rapidly to produce transient peaks in serum blood levels. For such antibiotics, gastric retention systems would be useful as they would be useful, as they would delay gastric emptying and release drug at a slower and constant rate.

Floating Drug Delivery Systems (FDDS) first described by Davis (1968), are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastroretention time and reduces fluctuations in plasma drug concentration. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00 mm. Thus multi-particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. Floating multi-particulate systems include: hollow microspheres (micro-balloons), low density floating micro-pellets and floating micro-beads. Hollow microspheres are in strict sense, spherical empty particles without core. The term microcapsule is defined as a spherical particle size varying from 50 nm to 2  $\mu$ m, containing a core substance. However the terms microcapsules and microspheres are often used synonymously.<sup>1-7</sup>

The rationale behind the use of GRDDS is shown in Figure 1.



**Figure 1: Rationale for the use of GRDDS**

### **Factors affecting gastric retention**

**Density:** Density of the dosage form should be less than the gastric contents (1.004gm/ml).

**Size:** Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to with those with a diameter of 9.9 mm.

**Shape:** The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT, 90 to 100% retention at 24 hours compared with other shapes.

**Fed or Unfed State:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. In fed state, MMC is delayed and GRT is considerably longer.

**Single or multiple unit formulation**<sup>8</sup>: Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage failure compared with single unit dosage forms.

**Nature of the meal:** Feeding of indigestible polymers of fatty acid salts can change motility pattern of stomach to a fed state, thus decreasing gastric emptying rate, prolonging drug release.

**Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

**Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

**Gender:** Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.<sup>8</sup>

**Age:** Elderly people, especially those over 70 years have a significantly longer GRT.

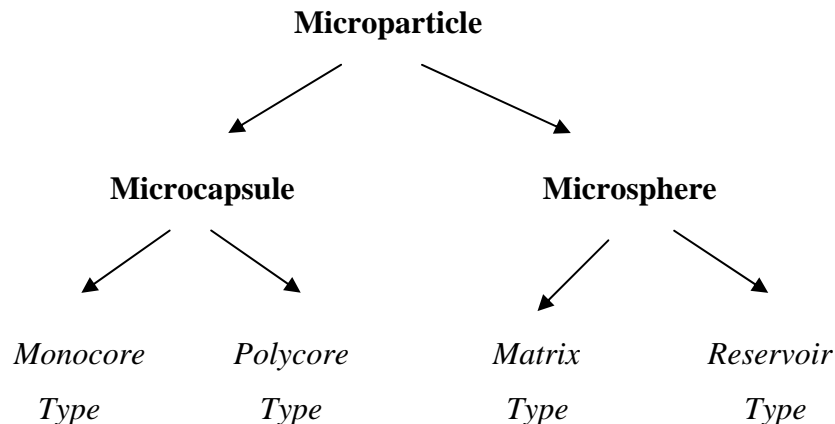
**Posture:** GRT can vary between supine and upright ambulatory states of the patients. 1.2.12

**Diseased state of the individual:** biological factors also affect the gastric retention e.g. Crohn's disease, gastrointestinal diseases and diabetes. Concomitant drug administration: Anti-cholinergics like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.<sup>9-10</sup>

**Suitable drug candidates for floating drug delivery system**

Sustained release in the stomach is useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 hr. In general, appropriate candidates for floating drug delivery system are the molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.<sup>11</sup>

- a) Drugs with narrow absorption window in GI tract, e.g., Para aminobenzoic acid, furosemide, riboflavin in a vitamin deficiency and Levodopa.
- b) Drugs which are primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Scinnarazine.
- c) Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- d) Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- e) Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate.

**a) Classification: Microparticle:**

Generally, the micro particulate delivery systems are intended for oral and topical use. The particles can be embedded within a polymeric or proteinic matrix network in either as solid aggregated state or a molecular dispersion, resulting in the formulation of microspheres. Alternatively, the particles can be coated by a solidified polymeric or proteinic envelope, leading to the formation of microcapsules. The ultimate objective of micro particulate-delivery systems is to control and extend the release of the active ingredient from the coated particle without attempting to modify the normal bio fate of the active molecules in the body after administration

and absorption. The organ distribution and elimination of these molecules will not be modified and will depend only on their physicochemical properties. Thus, the principle of drug targeting is to reduce the total amount of drug administered, and the cost of therapy while optimizing its activity.<sup>12</sup>

#### **b) ADVANTAGES**

- Improves patient compliance.
- Bio availability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
- Freedom from incompatibilities between drug and excipients especially with buffers.
- Better therapeutic effect of short half life drugs can be achieved.
- Gastric retention time is increased because of buoyancy.
- Site specific drug delivery to the stomach can be achieved.
- Mask the unpleasant odour, taste of drugs and protect the drugs from the environment.
- Freedom from incompatibilities between drugs and excipients especially the buffers and safe handling of toxic substances.
- Pulsatile release of antibiotics can alleviate evolution of the bacterial resistance. In the vaccine delivery, initial burst followed by delayed release pulses can mimic initial and boost injection, respectively.
- The local delivery system avoid systemic drug administration for local therapeutic effects and can reduce the related systemic side effects.
- The volatile drugs can be easily formulated as floating microspheres compared to other conventional dosage forms.
- The floating drug delivery formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found equally efficacious with medicaments which are absorbed from the intestine. Eg: chlorpheniramine maleate.<sup>13-18</sup>

#### **C) DISADVANTAGES**

- These systems require a high level of fluid in the stomach for drug delivery to float however this can be overcome by using low density polymers.

- The release rate of the controlled release dosage form vary from a variety of factors like rate of food transit through the drug.
- Potential toxicity due to loss of integrity of drugs.
- The dosage forms should be administered with more amount of water (200-250ml).
- Some drugs present in the floating system causes irritation to gastric mucosa.
- These dosage forms should not be crushed or chewed.<sup>14-17</sup>

#### **d) APPLICATIONS**

- Effective in delivery of sparingly soluble and in soluble drugs.
- Improve therapy of duodenal ulcers, gastritis and oesophagitis.
- The floating microspheres used as a carrier for drugs which have narrow absorption window like sulphonamides and cephalosporins.
- Hallow microspheres of NSAIDS reduces side effects.
- Microspheres have also found potential applications as injection, or inhalation products.<sup>18</sup>

#### **e) Uses:**

- Taste and odour masking
- Conversion of oil and other liquids, facilitating ease of handling.
- Protection of the drugs from the environment.
- Delay of volatilisation
- Freedom from incompatibilities between drugs and excipients, especially the buffers
- Improvement of flow properties
- Safe handling of toxic substances
- Dispersion of water insoluble substances on aqueous media
- Production of sustained release, controlled release and targeted medications.
- Reduced dose dumping potential compared to large implantable devices
- They facilitate accurate delivery of small quantities of potent drugs and reduced concentration of the drug at sites other than the target organ of tissue.<sup>19</sup>

## **2. TYPES OF MICROSPHERES**

- Magnetic microspheres
- Bioadhesive microspheres
- Floating microspheres
- Radioactive microspheres

### **Magnetic microspheres:**

This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials,

The different types are:

***Therapeutic magnetic microspheres:*** They are used to deliver chemotherapeutic agent to liver tumour. Proteins and peptides can also be targeted through this system.

***Diagnostic microspheres:*** These can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

### **Bioadhesive microspheres:**

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal, etc. can be termed as bioadhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

### **Floating microspheres:**

In floating types the bulk density is less than the gastric fluid so remains buoyant in stomach without affected by gastric emptying. The drug is released slowly at the desired rate by increasing gastric residence, if the system is floating on gastric content. Moreover it reduces chances of striking, dose dumping and also it produces prolonged therapeutic effect, therefore reduces dosing frequency.

### **Radioactive microspheres:**

Radio embolisation therapy microspheres sized from 10-30 nm which are larger than capillaries and get trapped in first capillary bed when they come across. So they are injected to the arteries that lead to tumour of interest.<sup>20,21,22</sup>

### **POLYMERS USED IN MICROSPHERES:**

Polymers used in the microsphere are generally classified into two types:

1. Synthetic polymers
2. Natural polymers

**Table (1): Classification of Polymer**

| <b>POLYMER</b>    | <b>SUB TYPES</b>                  | <b>EXAMPLES</b>   |
|-------------------|-----------------------------------|---|
| Synthetic polymer | Biodegradable                     | Lactides, Glycolides & their co polymers<br>Poly alkyl cyano acrylates<br>Poly anhydrides |
|                   | Non-biodegradable                 | Poly methyl methacrylate<br>Acrolein<br>Glycidyl methacrylate<br>Epoxy polymers           |
| Natural polymer   | Proteins                          | Albumin<br>Gelatin<br>Collagen  |
|                   | Carbohydrates                     | Agarose<br>Carrageenan<br>Chitosan<br>Starch  |
|                   | Chemically modified carbohydrates | Poly dextran,<br>Poly starch.   |

**Table (2) Various types of polymers and their application:<sup>24,25</sup>**

| <b>Polymer</b>                             | <b>Mechanism</b>                             |
|--|--|
| Modified starch,<br>HPMC,<br>Carbopol 974P | Slower release of drug.                      |
| Ethyl Cellulose                            | Controlled release for longer period of time |
| PLGA, Chitosan                             | Vaccine delivery                             |
| Chitosan coated PLGA microspheres          | Targeted drug delivery                       |
| Polyvinylalcohol, Polyacrylamide           | Adsorption of harmful substances in blood    |

**Mechanism of flotation of microspheres**

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.

**A. Mechanism of drug release from the microspheres**

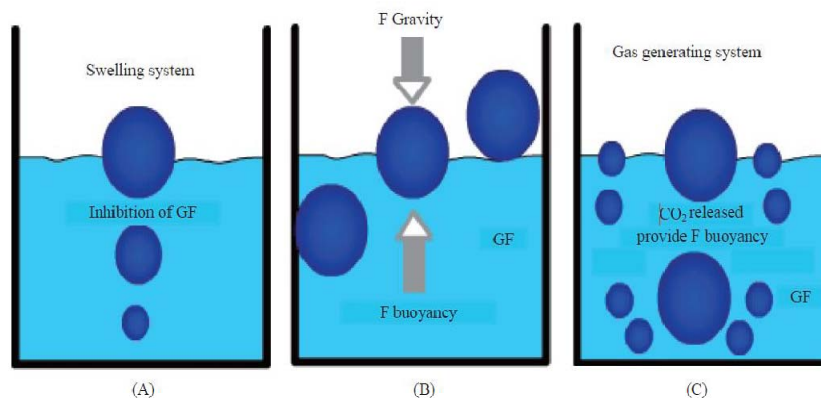
The mechanism of drug release from multiparticulates can occur in the following ways:<sup>11</sup>

1. 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.

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

3. 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 [26].



**Figure 2: Mechanism of floating systems (A) Swelling system (C) Gas generating system**

## METHOD OF PREPARATION

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by microencapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release, method of cross linking, evaporation time and co-precipitation, etc. The various methods of preparations are:

A. Emulsion Solvent Evaporation Technique

B. Emulsion Cross Linking Technique

C. Emulsion-Solvent Diffusion Technique

D. Emulsification Heat Stabilizing Technique

E. Co-acervation Phase Separation Technique

a) Thermal Change

b) Non-Solvent Addition

c) Polymer Addition

d) Salt Addition

e) Polymer-Polymer Interaction

F. Spray Drying Technique

G. Polymerisation Technique

a) Normal polymerisation

b) Interfacial polymerisation

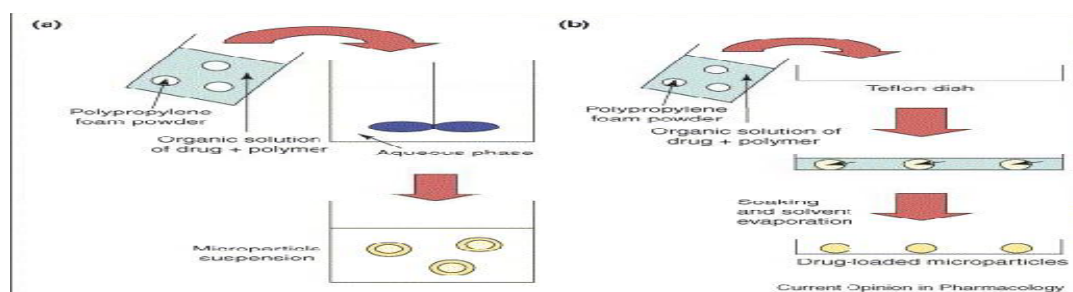
H. Ionic Gelation Technique

I. Hydroxyl Appetite (HAP) Microspheres In Sphere Morphology

J. Hot Melt Microencapsulation technique

### A. Emulsion Solvent Evaporation Technique

In this technique the drug is dissolved in polymer which is previously dissolved in chloroform and the resulting solution is added drop wise to aqueous phase containing 0.2% of PVP as emulsifying agent and agitated at 500 rpm, then the drug and polymer solution transformed into fine droplet which solidifies into rigid microspheres and then collected by filtration, washed with demineralised water. Finally desiccated at room temperature for 24 hrs.<sup>27</sup>



**Fig.3 Emulsion Solvent Evaporation Technique**

### B. Emulsion Cross Linking Technique

In this method, drug is dissolved in aqueous gelatine solution which is previously heated for 1 hr. at 40 °C. The solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35°C, which results in w/o emulsion further stirring is done for 10 min at 15°C. Then the microspheres are washed with acetone and isopropyl alcohol. Further air dried and dispersed in 5ml of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs. for cross linking and treated with 100ml of 10Mm glycine solution containing 0.1%w/v of tween 80 at 37 °C for 10 min to block unreacted glutaraldehyde<sup>28</sup>.

### C. Emulsion-Solvent Diffusion Technique

In order to improve the residence time in colon floating microparticles of drug is prepared by emulsion solvent diffusion technique. The drug polymer mixture is dissolved in a mixture of

ethanol and dichloromethane (1:1) then the mixture is added drop wise to sodium lauryl sulphate (SLS) solution. The solution is stirred with propeller type agitator at room temperature at 150 rpm for 1 hr, washed and dried in a desiccator at room temperature<sup>29</sup>.

#### **D. Emulsification Heat Stabilizing Technique**

In this method, drug and polymer are dissolved in 20 ml of deionised water and 5 ml of egg albumin solution and 0.1% of Tween-80 are added stirred it for 30 min. The prepared solution is used as aqueous phase. The oil phase is prepared by mixing 20 ml of sunflower oil and 5ml of diethyl ether with 1% span-80 (as emulsifier) and stirred it for 20 mins at 800-1000 rpm on a magnetic stirrer. The primary emulsion is prepared by adding the oil phase drop wise to the aqueous phase followed by stirring it for 30 mins at 800-1000 rpm. The prepared primary emulsion is added to pre-heated (65 to 70°C) sunflower oil (80 ml) by using 21 No. needle and stirred at 1000-1200 rpm for 2 hrs till the solidification of microspheres takes place. The suspension then allowed to cool to room temperature with continuous stirring using a magnetic stirrer. On cooling, 100 ml of anhydrous ether is added. The suspension containing the microspheres is centrifuged for 15 mins and the settled microspheres are washed three times with ether to remove traces of oil on microspheres surfaces. The obtained microspheres are then vacuum dried in a desiccator overnight and stored at 4°C in dark<sup>30</sup>.

#### **E. Co-acervation Phase Separation Technique**

a) *Thermal Change*: Microspheres are formed by dissolving polymer (ethyl cellulose) in cyclohexane with vigorous stirring at 80 °C by heating. Then the drug is finely pulverized and added to the above solution with vigorous stirring. The phase separation is brought about by reducing temperature using ice bath. The product is washed twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule<sup>31</sup>.

b) *Non Solvent Addition*: Microspheres are formed by dissolving polymer (ethyl cellulose) in toluene containing propyl-isobutylene in a closed beaker with stirring for 6 hrs. at 500 rpm and the drug is dispersed in it. Stirring is continued for 15 mins., then phase separation is brought about by petroleum benzene with continuous stirring. The microcapsules washed with n-hexane and air dried for 2 hrs., and kept in an oven at 50°C for 4 hrs.

c) *Polymer Addition*: Microspheres are formed by dissolving polymer (ethyl cellulose) is dissolved in toluene, then 1 part is added to 4 parts of crystalline methylene blue hydrochloride.

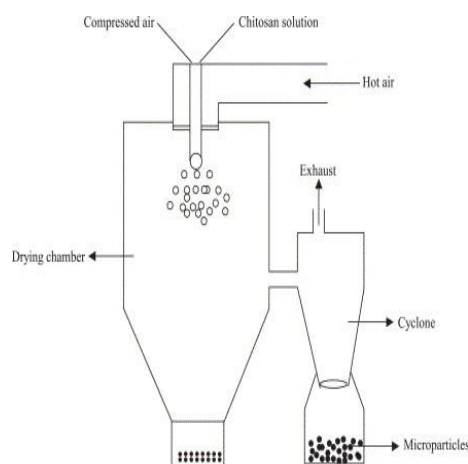
Co-acervation is accomplished by adding liquid polybuta-diene. Then the polymer coating is solidified by adding a nonsolvent (hexane). The resulting product is washed and air dried.

d) *Salt Addition*: Microspheres are formed by dissolving oil soluble vitamin in corn oil and is emulsified by using pig skin gelatin under condition of temperature 50° C, coacervation is induced by adding sodium sulphate. Stirring is necessary for uniform coating of gelatin. The resultant microspheres product is collected and washed with water, chilled below gelation temperature of gelatin and dried by using spray drying.

e) *Polymer-Polymer Interaction*: In this process, aqueous solution of gum Arabica and gelatin (isoelectric point 8.9) are prepared, the homogeneous polymer solutions are mixed together in equal amount, diluted to about twice their volume with water, adjusted to pH 4.5 and warmed to 40- 45°C. the oppositely charged macromolecules interact at these conditions and undergo coacervation. While maintaining the warm temperature, the liquid core material (methyl salicylate) is added to polmer solution and stirred well. Then the mixture is cooled to 25°C and coating is rigidised by cooling the mixture to 10°C.

## F. Spray Drying Technique

This method is used to prepare polymeric blended microspheres loaded with drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent. Organic solution of poly epsilon-caprolactone (PCL) and cellulose acetate butyrate (CAB), in different weight ratios with drug is prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may loose crystallinity due to fast drying process<sup>28</sup>.



**Fig.4 Spray Drying Technique**

## **G. Polymerization Techniques**

Mainly two techniques are used for the preparation of microsphere by polymerization technique:

### **(a) Normal polymerization:**

Normal polymerization classified as:

1. Bulk polymerization
2. Suspension/ pearl polymerization
3. Emulsion polymerization

1. In *bulk polymerization*, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer 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.

2. *Suspension polymerization* is carried out at lower temperature and also referred to as pearl polymerization in which the monomer mixture is heated with active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less 100µm.

3. *Emulsion polymerization* differs from the suspension polymerization due to presence of initiator in aqueous phase and also carried out at low temperature as suspension. External phase normally water in last two techniques so through which heat can be easily dissipated. The formation of higher polymer at faster rate is possible by these techniques but sometimes association of polymer with the un- reacted monomer and other additives can occur.

### **(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 dissolved in continuous phase while other is dispersed in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of the solubility of formed polymer in the emulsion droplet. The formation is *Monolithic*, if the polymer is soluble in droplet and the formation is *Capsular type* if the polymer is insoluble in droplet<sup>32,33</sup>.

## **H. Ionic Gelation Technique**

In this technique polymer is dissolved in purified water to form a homogeneous polymer solution. The core material (drug) as fine powder passed through mesh no.120, is added to the

polymer solution and mixed to form a smooth viscous dispersion. This dispersion is added drop wise into 10%w/v CaCl<sub>2</sub> solution through a syringe with a needle of diameter 0.55mm. The added droplets are retained in CaCl<sub>2</sub> solution and allowed to cure for 20 minutes at 200 rpm to produce spherical rigid microsphere. Finally the microspheres are collected and dried in an oven at a temperature 45°C for 12 hrs.<sup>34</sup>

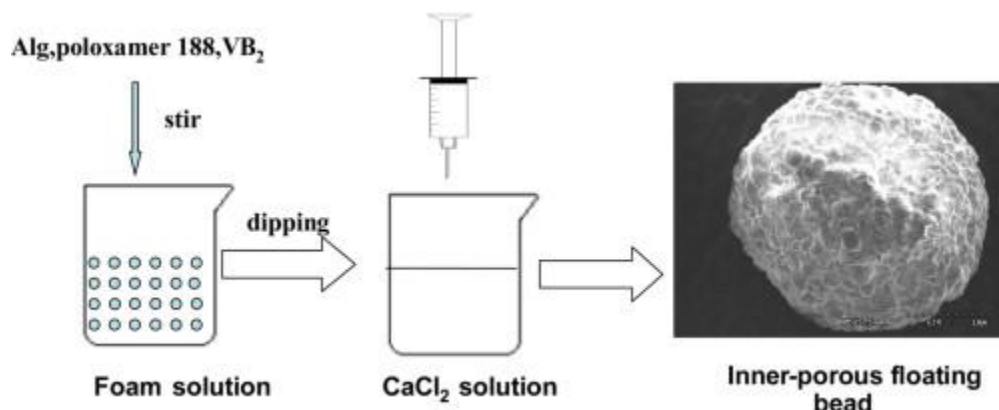


Fig.5: Ionic Gelation Technique

### I. Hydroxyl Appetite (HAP) Microspheres in Sphere Morphology

In this method, initially HAP granules obtained by precipitation method followed by spray drying process. Microspheres are prepared by oil-in-water emulsion followed by solvent evaporation technique. Oil-in-water emulsion obtained by dispersing the organic phase (dichloromethane solution containing 5% of EthyleneVinylAcetate and appropriate amount of HAP) in the aqueous medium of the surfactant. While dispersing in aqueous phase, the organic phase is transformed into tiny droplets and each droplet surrounded by surfactant molecules. The protective layer thus formed on the surface which prevents the droplets from coalescing and helps to stay individual droplets. While stirring, dichloromethane (DCM) is slowly evaporated from the droplets and after the complete removal of DCM, the droplets solidifies to become individual microspheres. The size of the droplets formed depends on many factors like types and concentration of the stabilizing agents, type and speed of stirring employed, etc, which in turn affects the size of the final microspheres formed<sup>35</sup>.

### J. Hot Melt Microencapsulation Technique

The polymer is first melted and then mixed with solid particles of the drug that has been sieved to less than 50 µm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the

emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, *e.g.* polyanhydrides. Microspheres with diameter of 1-1000  $\mu\text{m}$  can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed<sup>36</sup>.

#### **EVALUTION TESTS FOR FLOATING MICROSPHERES :**

- A. Particle size.
- B. Tapped density.
- C. Percentage yield.
- D. Swelling index.
- E. Buoyancy.
- F. Drug entrapment efficacy.
- G. Iso electric point.
- H. Fourier transform infrared stability studies (FTIR).

#### **PARTICLE SIZE:**

Particle size is measured by using optical microscopy by measuring the mean particle size of 200-300 particles with the help of calibrated optical micrometre. Particle size is determined by optical microscopy using a quantity of dried microspheres suspended in glycerin<sup>37</sup>.

#### **TAPPED DENSITY:**

Tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus.<sup>38</sup>

Tapped density = mass of microspheres / volume of microspheres after packing.

Compressibility index:  $I = \frac{v_b - v_t}{v_b} \cdot 100$

Where  $v_b$  = bulk volume.

$v_t$  = tapped volume.

#### **PERCENTAGE YIELD :**

The percentage yield can be calculated by using the following formula.

$$\text{Percentage yield} = \frac{\text{Actual weight of floating microspheres}}{\text{Total weight of excipients and drug}} \times 100$$

**SWELLING INDEX:**

Swelling index is determined by measuring the extent of swelling of microspheres in a particular solvent. To ensure the complete equilibrium, exactly weighed 100 mg of microspheres are allowed to swell in solvent for 34 hrs. The excess surface adhered liquid drops are removed by blotting and the swollen microspheres are weighed by using microbalance. The Hydrogel microspheres then dried in an oven at 60° for 5 hrs. until there is no change in the dried mass of sample. The swelling index of the microsphere is calculated by using the formula:

$$\text{Swelling index} = \frac{\text{mass of swollen microspheres} - \text{mass of dried microspheres} \times 100}{\text{mass of dried microspheres}}$$

**BUOYANCY:**

To assess the floating properties, the microspheres were placed in 0.1 N hydrochloric acid containing 0.02 % v/v Tween 80 surfactant to gastric conditions. Tween (0.02% v/v) was used to impart wetting effect of the natural surfactants such as phospholipids in the GIT.

The buoyancy was calculated by

$$\text{Buoyancy (\%)} = \frac{W_f}{(W_f + W_s)} \times 100$$

Where,  $W_f$  = weight of floating micro spheres,

$W_s$  = weigh of the settled microspheres.

**ENTRAPMENT EFFICACY:**

The entrapment efficacy of drug can be measured by dissolving the powdered micro spheres in 0.1N HCl and analysed spectrometrically at particular wave length using calibration curve<sup>38</sup>.

$$\text{Entrapment efficiency} = \frac{\text{actual drug content}}{\text{theoretical drug content.}}$$

**ISO ELECTRIC POINT :**

The isoelectric point of can be measured by using micro electrophoresis apparatus by measuring electrophoretic mobility of microspheres. The mean velocity o at different pH values from 3-10 is calculated by measuring the time of particle movement over a distance of 1nm.

**FTIR (Fourier Transform Infra-Red) :**

The drug - polymer interaction and also degradation of drug while processing for microspheres can be determined by FTIR.

**SCANNING ELECTRON MICROSCOPY:** The surface morphology and particle size of microspheres are determined by Scanning Electron Microscopy. Dry microspheres are placed in

a scanning electron microscope brass stub and coated with gold in an ion sputter. Picture of microspheres are taken by random scanning of the stub.

### **STABILITY STUDIES:**

Microspheres are tested for stability. The preparations are divided into 3 sets and are stored at 4° (refrigerator), room temperature and 40° (thermostatic oven). After 15, 30 and 60 days, drug content of all the formulations is determined by entrapment efficiency technique.

### **In- Vitro RELEASE STUDIES:**

To carry out the *in vitro* drug release, accurately weighed drug-loaded microspheres are dispersed in dissolution medium in a beaker and maintained at 37±2° under continuous stirring at 100 rpm. At selected time intervals 5 ml samples are withdrawn through a hypodermic syringe fitted with a 0.4 mm Millipore filter and replaced with the same volume of pre-warmed fresh dissolution medium to maintain a constant volume of the receptor compartment. The samples are analyzed spectrophotometrically.

### **CONCLUSION**

Gastro retentive microsphere have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. Microsphere drug delivery systems provide several all the advantages including greater flexibility and adaptability of microsphere dosage forms which gives clinicians and those engaged in product development powerful new tools to optimize therapy. The increasing sophistication of delivery technology will ensure the development of increasing number of gastroretentive drug delivery systems to optimize the delivery of molecules that exhibit narrow absorption window, low bioavailability and extensive first pass metabolism. It is little wonder therefore, that such systems are growing rapid in popularity. The control of gastro intestinal transit could be the focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patient.

### **REFERENCES**

1. Hirtz J. The GIT absorption of drugs in man: a review of current concepts and methods of investigation. *Br J Clin Pharmacol*. 1985; 19:77S-83S.
2. Nasa P, Mahant S and Sharma D. Floating Systems: A Novel Approach towards Gastroretentive Drug Delivery System. 2010;2: 1-7.
3. Sharma V, Singh L, Sharma V. A Novel approach to combat regional variability: Floating drug delivery system. *IJPSRR*. 2011; 8(2):154-159.

4. Hilton, A.K.Deasy, P.B., J.Pharma.Sci. 82(7),737,1993.
5. Dhole AR, Bankar VH, Pawar SP. A Review on Floating Multiparticulate Drug Delivery System- A Novel Approach to Gastric Retention. IJPSRR. 2011; 6(2): 205-211.
6. Somwanshi SB, Dhamak KB and Khadse AN. Floating Multiparticulate Oral Sustained Release Drug Delivery System. J.Chem.Pharm Res. 2011; 3(1): 536-547.
7. Vyas SP, Khar RK. Targeted & Controlled Drug Delivery. New Delhi: CBS Publishers and Distributers; 2002:417-457.
8. Arora S, Ali J, Ahuja A, Khar RK and Baboota S. Floating Drug Delivery Systems: A Review.AAPS PharmSciTech. 2005; 6(3):E372-E390.
9. Bhowmik D, Chiranjib B, Margret C, Jayakar B and Sampath K.P. Floating drug delivery system: A Review, Der Pharmacia Lettre. 2009; 1(2): 199-218.
10. Garg R and Gupta G.D. Progress in controlled gastroretentive delivery. Trop J Pharm Res. 2008; 7(3):1055-1066.
11. Bakan JA., "Microencapsulation: Theory And Practice Of Industrial Pharmacy": 3<sup>rd</sup> edition , Bombay (India): Varghese publishing company", 1987:453-455
12. Gurang patel Ajay Tiwari. Floating microspheres as a noval root for H2 blocker. Nirav Rabadia Jaipur National University, Jagatpur, Jaipur(Rajastan) India. IJRP 3(2); 45-52.
13. Shivkumar HG, Vishakanteguda and D pramod kumar TM. Ind J Pharm Education 2004; 38(4):172-179.
14. Oja G, Tanwar YS, Chanuhan CS and Nawka PS. Floating microspheres; Development, Charecterization and Applications. <http://www. Pharma info. Net/review on Floating microspheres Development- Character and applications>.
15. Talukder R, Fissihi R. Drug Development and Ind Pharm 2004; 30(10):1019-1028.
16. Katariasahill, Ajaybilendi and Bhawanakapoor. Microsphere; a review. International Journal of Research in Pharmacy and Chemistry 2001; 1(4): 2231-2781.
17. Alagusundaram M., Microspheres As A Novel Drug Delivery System. International Journal of Chem Tech Research 2009; 1(3): 526-534.
18. James swarbrick, "Encyclopedia of Pharmaceutical Technology", Vol. (1) 3rd edition, Informa Health Care USA, Inc.,2007: 2330-2333
19. Li, S.P., Feld K.M., Grim W.M., "Recent Advances in Microencapsulation Technology and Equipment", Drug Development and Industrial Pharmacy, 1988; Vol. 14: 353-376.

20. Patel JK, Patel RP, Amin AF, Patel MM, "Bioadhesive Microspheres- Review" [www.pharmainfo.net/ review](http://www.pharmainfo.net/review), 2010; Vol 4(6).
21. Shanthi N.C., "Traditional and Emerging Applications of Microspheres: A Review", International Journal of PharmaTech Research, 2010; Vol.2(1):675-681.
22. Yadav AV., Mote HH., "Biodegradable Starch Microspheres for Intranasal Delivery", Indian Journal of Pharmaceutical Sciences, 2008; Vol 70 (2):170-174
23. Jain A. New Concept: Floating Drug Delivery System. IJNDD. 2011; 3(3):162-169.
24. Patel DM, Patel MJ, Patel CN. Multi Particulate System: A Novel Approach in Gastro-Retentive Drug Delivery. IJAPR. 2011; 2(4): 96-106.
25. Dey NS, Majumdar S and Rao MEB. Multiparticulate Drug Delivery Systems for Controlled Release. Trop J Pharm Res. 2008; 7(3):1067-1075.
26. Trivedi P., Verma A.M.L., Garud N., "Preparation and Characterization of Acclofenac Microspheres": Asian Journal of Pharmaceutics, 2008; vol2 (2): 110-115.
27. Dandagi MP., Gadad P.A., Iliger R.S., "Mucoadhesive Microspheres of Propranolol Hcl for Nasal Delivery", Indian Journal Of Pharmaceutical Sciences, 2007; Vol 1(3):402-407.
28. Mathew Sam T., Devi Gayathri S., Prasanth V.V., Vinod B; "NSAIDs as Microspheres," The Internet Journal of Pharmacology, 2008; Vol 6(1).
29. Y. Phalgun, "HPMC Microspheres of Zidovudine For Sustained Release", International Journal of Pharmacy and Pharmaceutical Sciences, 2010; Vol. 2( 4): 41-43.
30. Leon lackmann, "Theory And Practice of Industrial Pharmacy", 2009: (420-424).
31. Jain N K, "Controlled and Novel drug delivery", (2004), 236- 237.
32. Jayaprakash S, Halith S M, Mohamed Firthouse P U, Kulaturanpillai K, Abhijith, Nagarajan M., "Preparation And Evaluation of Biodegradable Microspheres Of Methotrexate", Asian Journal of Pharmaceutical sciences, 2009; Vol. 3: 26-29.
33. Tirupati M. Rasala, "Study of Ionotropic Gelation Technique To Entrap Diltiazem HCl In Microparticulate System" ., Journal of Pharmacy Research 2010; Vol.3(7):1531-1534.
34. T S Pradesh., "Preparation of Microstructured Hydroxyapatite Microspheres Using Oil In Water Emulsions", Bulletin Mater Science, 2005; Vol. 28(5): 383-390.
35. Harshad Parmar, "Different Methods Of Formulation And Evaluation Of Mucoadhesive Microsphere," International Journal Of Applied Biology And Pharmaceutical Technology, 2010; Vol 1(3):1157-1167

36. Punitha K, Kadhira S, Umadevis K, Vaijayanti V, Padma priya S, Suresh kumar S. International Journal of Pharmacy and Pharmaceutical Council 2010; 2(4): 0975-1491.
37. Pahwa R, Neeta, Bhagwan S, Kumar V, Kohli K. Floating microspheres; an innovative approach for gastric retention. Der Pharmacia Letter 2010; 2(4): 461-475.