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Gastro Retentive Floating Microspheres a New Trend of Drug Delivery System

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ABSTRACT

The purpose of writing this review on microspheres is to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. Microsphere promises to be a potential approach for gastric retention. Floating drug delivery systems are designed for the poorly soluble, unstable and locally acting drugs in the G.I.T and they have low bulk density than the gastric content also they float in the stomach for a prolonged period of time. From this the designing of 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. In the floating microspheres, the drug loaded microspheres come in contact with gastric fluid the gel formers, and polymer hydrates to form a colloidal gel barrier then controls the rate of fluid penetration into the device and consequent drug released by the swollen polymer lowers the density and float in the stomach.

Keywords: FDDS; Floating Microspheres; Sustained Release; Gastric Emptying Time.

1.0 Introduction

Now days the oral route represents the predominant and most preferable route for drug delivery for the administration of therapeutic agents. Numerous oral extended release drug delivery systems have been developed to prolong drug release.

An important prerequisite for successful performance for an oral extended release drug delivery system is that the drug should have good absorption throughout the whole gastrointestinal tract (GIT) to ensure continuous absorption of released drug (Chawla et al.2003; Hwang et al., 1998).

But for large number of drugs, transport across the intestinal epithelium in each segment of GIT is not uniform and often limited to a particular segment (window) only. So, the oral extended release drug delivery becomes more difficult due to the inability to restrain and localize the drug delivery system within the Under such conditions, one of the most feasible approach for achieving a prolonged and

predictable drug delivery profile in GIT is to control the gastric residence time by designing a delivery system that is able to reside in stomach or preferably prior to absorption window that would increase the absorption of drugs.

The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance (Fell,1996; Streubel et al., 2006; Dave et al.,2005).

These considerations have led to development of unique oral controlled release dosage forms with gastro retentive properties shown in a figure no 1

1.1 Gastroretentive Drug Delivery Systems

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery system (GRDDS).

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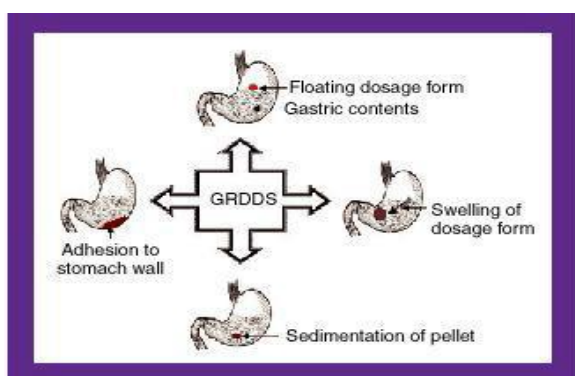
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These are the systems which can remain in gastric region for several hours the drug there in a controlled & prolonged manner, so that the drug could be supplied continuously to absorption site in GIT (Nayak et al., 2010). and significantly prolongs the gastric residence time of drug. After oral administration, such a delivery system would be retained in stomach. It will release

Fig. 1. Different Approaches of Gastric Retention



1.1.1 Drug Candidates For Gastric Retention

The rationale for the selection of active pharmaceutical ingredients for fabrication as a GRDDS is described in

Table 1.

Rationale for gastro-retention	Name of drug
Narrow absorption window at upper part of GIT (Hoffman et al., 2004; Klausner et al., 2003)	Levodopa, Atenolol, Theophylline, Riboflavin, Repaglinide, Diltiazem, Risedronate
pH dependent absorption from stomach (acidic drugs) (Ozdemir et al., 2000; Parikh and Amin, 2008)	Furosemide
Degradation at higher pH (higher stability at lower pH) (Robles et al., 2008; Srivastava et al., 2005)	Captopril
Degradation in intestine or colon (Basit and Lacey, 2001)	Ranitidine hydrochloride
Higher solubility at lower pH or weakly basic drugs (Soppimath et al., 2001)	Cinnarizine, Diazepam, Verapamil, Cefpodoxime proxetil, Dipyridamole, Rosiglitazone maleate
Drugs for local action – antacids, anti-ulcer drugs, antibacterial for <i>H. pylori</i> infection (Bardonnet et al., 2006; Whitehead et al., 2006)	Misoprostol, Clarithromycin, Metronidazole, Amoxicillin

Gastro retentive DDS, on the other hand, are not suitable for drugs that:

- May cause gastric lesions, e.g. NSAIDs
- Are unstable in the strong acidic environment of the stomach.
- Have very limited acid solubility e.g. phenytoin etc.
- Intended for selective release in the colon.

E.g. 5-amino salicylic acid and corticosteroids. In addition, gastro retentive systems do not offer significant advantages over conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract

2.0 Classification of Micro Spheres

Based on the type of microparticle [11]:

Micro capsule:

A. Micro capsule: monocoire type, polycore type.

B. Micro sphere: matrix type, Reservoir type. The micro particle delivery systems are intended for oral and topical use.

A. Micro capsule: The microparticles are coated by a solidified polymeric or proteinic envelop, leading to the formation of micro capsules.

B. Micro sphere: The particles enclosed with in a polymeric or proteinic matrix network in either as a solid aggregated state or molecular dispersion leading to the formation of microspheres.

Based on the method of formulation [12] :

A. Effervescent floating micro particles:

- Gas generating systems.
- Volatile liquid/ vacuume containing systems.

B. Non Effervescent floating micro particles.

A. Effervescent floating microparticles:

These are matrix type prepared with the help of swell able polymers. These floating micro particles release Co₂ when they are come in contact with the gastric contents and become entrapped in swollen hydrocolloids.

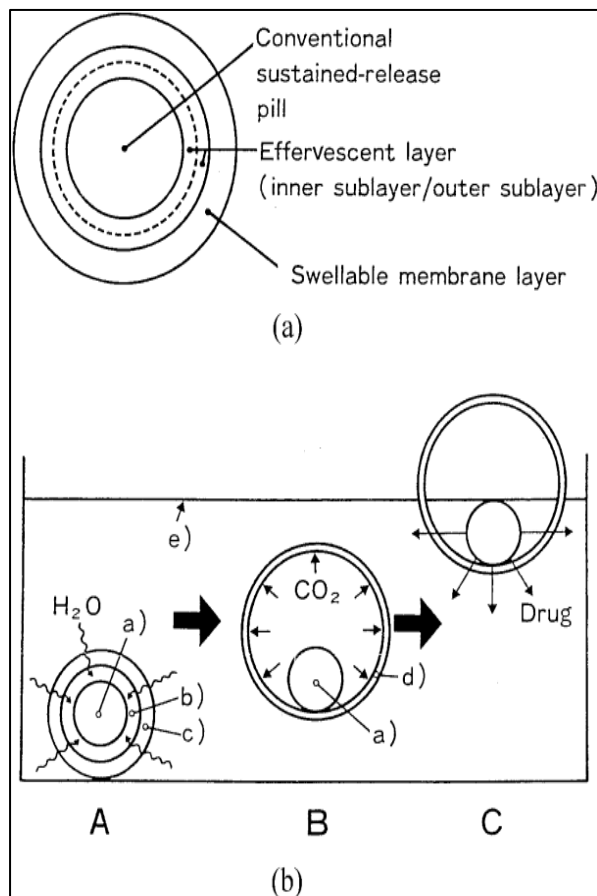
The polymers used are methyl cellulose, HPMC, chitosan and various effervescent compounds like sodium bicarbonate, tartaric acid, citric acid. Effervescent micro spheres are further classified into: Gas generating systems had shown in figure -2(b) and volatile liquid or vacuum containing systems.

Gas generating systems:**1 Intra gastric single layer floating micro spheres:** these are formulated by intensively mixing with CO_2

generating agents and drug within the matrix micro sphere. The drug is slowly released at a desired rate from the floating system and after complete release the residual system is expelled from stomach, this leads to a better gastric retention time and better control over fluctuations in plasma drug concentration.

- **Intra gastric bi layer floating micro spheres:** These systems contain two polymer layers out of which one is immediate release layer and another one is sustained release layer.

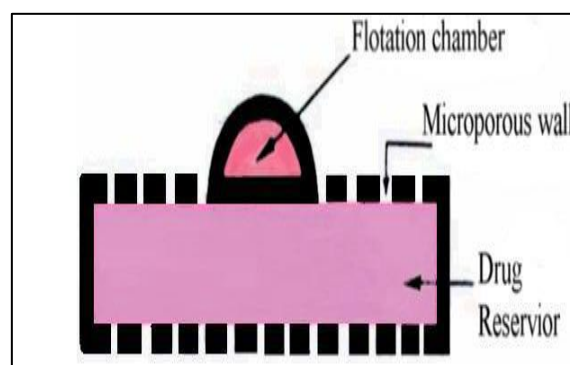
Multiple type of floating pills: these systems consist of sustained release pills as seeds surrounded double layer. The inner layer consists of effervescent agents while outer layer is Swellable membrane layer shown in figure 2(a). When these pills come in contact with gastric fluid it sinks at once and then forms swollen pills like balloons, which float as they have lower density due to generation and entrapment of CO_2 within the system

Fig: 2.**(A) A multiple-unit oral floating dosage system.****(B) Stages of floating mechanism:**

- (A) Penetration of water;
- (B) Generation of CO_2 and floating;
- (C) Dissolution of drug. Key:

(a) Conventional SR pills**(b) Effervescent layer****(c) Swellable layer****(d) Expanded Swellable membrane layer****(e) Surface of water in the beaker (37°C).****Volatile liquid/ vacuume containing systems:**

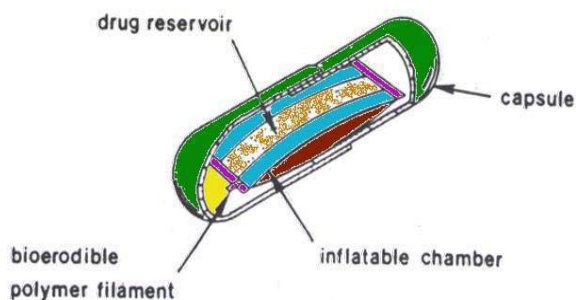
Intra gastric floating System: These systems can be made to float in the stomach due to the presence of a floating chamber, which may be a vacuum filled with air or a harmless gas. The drug reservoir is encapsulated in a microporous compartment having pores along its top and bottom surfaces. The peripheral wall of the drug avoids the contact of drug with gastric contents and the floatation chamber allows the floating of micro sphere in the gastric environment shown in figure no 3

Fig: 3.

Inflatable gastro intestinal delivery system: these systems are fabricated by loading the inflatable chamber with a drug reservoir which can be impregnated polymeric matrix then encapsulate in a gelatin capsule.

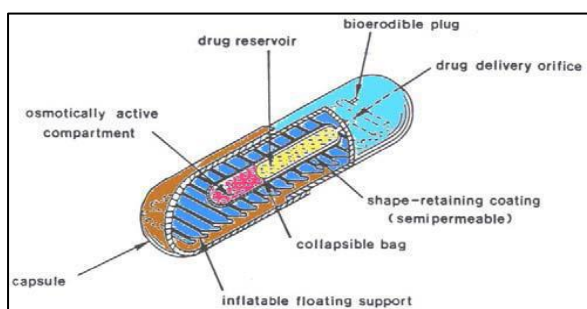
After administration, the inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. This inflatable device comprises of an inflatable member in a deflated state connected to an inflation tube and one or two cartridges which are capable of delivering the drug into the GI tract. This system is shown in figure-4

Fig: 4.



Intra gastric osmotically controlled drug delivery systems: It contains an osmotically pressure controlled drug delivery device and inflatable floating support in a biodegradable capsule, when this capsule come in contact with gastric contents it disintegrate quickly to release the intra gastric osmotically drug delivery device. The osmotically pressure controlled drug delivery device consists of two compartments one is drug reservoir compartment enclosed by a pressure responsive collapsible bag and other one is osmotically active compartment consists of osmotically active salt enclosed with in a semi permeable membrane. The osmotic pressure is created due to continuous absorption of GI fluid into osmotically active compartment through semi permeable membrane. Thus created osmotic pressure acts on the collapsible bag and in turn result in the reduction of compartment volume and activates drug release through delivery orifice, as shown in figure-5. Osmotic controlled floating system comprised of hallow deformable unit that was convertible from a collapsed to an expanded position after an extended period of time. Housing was attached to the deformable unit and it was internally divided into first and second chamber and these are separated by an impermeable pressure responsive movable bladder. The first chamber consist active drug and the second chamber consists of volatile liquid such as cyclopentane or ether that vaporizes at body temperature to produce a gas enabling the drug reserve to floating

Fig: 5.



b- Noneffervescent floating micro particles: these are prepared by using a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, matrix forming polymers like polycarbonate, polycrylate, polymethacrylate and polystyrene. When these type of particle are come in contact with gastric fluids attains bulk density less than 1 and the entrapped within the swollen gel like structure act as reservoir and allows sustained release of drug through gelatin mass. These are further classified into

- **Single layer floating micro spheres:** These are formulated by intimate mixing of drug with a gel forming hydrocolloids which swells when come in contact with gastric fluid and maintain bulk density of less than unity.
- **Bi layer floating micro spheres:** These contain two layers one is immediate release containing misoprostil layer and second one is sustained release layer which buoyant in stomach by absorbing gastric fluid. This type of dosage forms remain in buoyant for period of time about 13 hours.
- **Alginate beads:** These are prepared by dropping sodium alginate solution into an aqueous solution of calcium chloride resulting in the preparation of spherical alginate beads having 2.5mm diameter. These systems remain buoyant for 12 hours and have prolonged release time of more than 5.5 hours.
- **Hallow micro spheres:** These are prepared by emulsion solvent evaporation technique in which the drug is enclosed in outer polymer hell resulting the sphere.

Advantages [13-16]

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 buffer
- 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 malatone

Disadvantages[14-17]:

- 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.

Applications [18]

- 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.
- Hollow microspheres of NSAIDS reduces side effects.
- Microspheres have also found potential applications as injection, or inhalation products.

Polymers Used In Floating Microspheres [19]

The polymers used in the preparation of floating microspheres are

1. Synthetic polymers.
2. Natural polymers

Polymer	Sub Type	Examples
Synthetic polymer	Biodegradable	Lactides, glycosides and their co polymers. Poly alkyl cyanoacrylates, Polyanhydrides
	Non-biodegradable	Polymethyl methacrylate, Acrolin, Glycidyl methacrylate, Epoxy polymers
Natural polymer	Proteins	Albumin, Gelatin, Collagen
	Carbohydrates	Agarose, Carragenan, Chitosan, Starch.
	Chemically modified carbohydrates.	Poly dextrans, Poly starch

Polymers and Their Applications [20-22]

Polymer	Application
Modified starch, HPMC, Carbapol 974p	Slower release of drug.
Ethyl cellulose	Controlled release for longer period of time.
PLGA, chitosan	Vaccine delivery.
Chitosan coated PLGA polymers	Targeted drug delivery.
Polyvinylalcohol, Polyacryldine	Adsorption of harmful substance in blood

Methods Of Preparation Of Microspheres [23]

The floating microspheres are the gastro retentive drug delivery systems which releases the drug in controlled and sustained manner. These floating systems are formulated by using low density and Swellable polymers, gel forming agents. When these systems come in contact with the gastric fluid they form barrier and releases the drug in controlled manner. The following methods are used for the preparation of floating microspheres.

- A. Emulsion Solvent Evaporation Technique
- B. Emulsion Cross Linking Technique
- C. Emulsion-Solvent Diffusion Technique
- D. Emulsification Heat Stabilizing Technique
- E. Multiple emulsion method.
- F. Co-acervation Phase Separation Technique

- a) Thermal Change
- b) Non-Solvent Addition
- c) Polymer Addition
- d) Salt Addition
- e) Polymer-Polymer Interaction

G. Spray Drying Technique

H. Polymerisation Technique

a) Normal polymerisation

b) Interfacial polymerisation

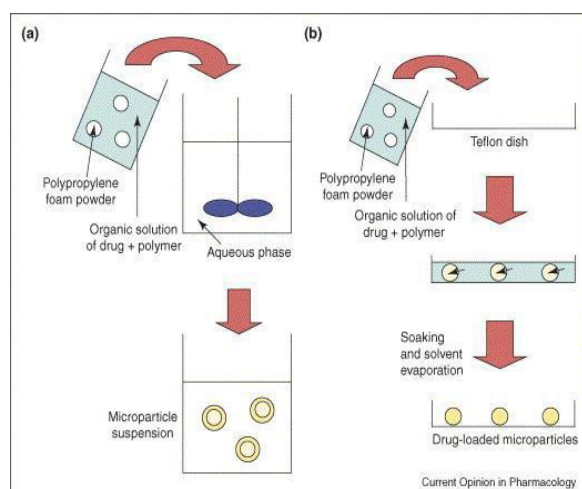
I. Ionic Gelation Technique

J. Hydroxyl Appetite (HAP) Microspheres In Sphere Morphology

A. Emulsion Solvent Evaporation Technique [24] :

Solvent evaporation involves the formation of an emulsion between polymerisation and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. This process is carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution, with agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrink around the core. If the core material is dissolved in the coating polymer solution/ matrix type microcapsules are formed as shown in figure-

6(a). The core material may be either water soluble or water insoluble materials.



B. Emulsion Cross Linking Technique [25-26]

The micro particulate carrier of natural polymers like proteins and carbohydrates are prepared by using this method. The natural polymers

are dissolved or dispersed in aqueous medium followed by in non-aqueous medium oil otherwise; the drug is dissolved in aqueous gelatine solution which is previously heated for 1hr. at 40 oC. The solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35oC, which results in w/o emulsion further stirring is done for 10min at 15o C. Then the microspheres are washed with acetone and isopropyl alcohol. The cross linking is achieved either by means of heat or by using chemical cross linkers. 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 37o C for 10 min to block unreacted glutaraldehyde. The chemical cross linking agents used are glutaraldehyde, formaldehyde, acid chloride; the heat denaturation is not suitable for thermolabile substances. The main disadvantage of this method is excessive exposure of active ingredients to chemicals, when they are added at the time of preparation and then subjected to centrifugation, washing and separation. The natural surfactants used to stabilise the emulsion phase can greatly influences the size, size distribution, surface morphology, loading, drug release and bio performance of the final multi particulate product.

C. Emulsion-Solvent Diffusion Technique [27]

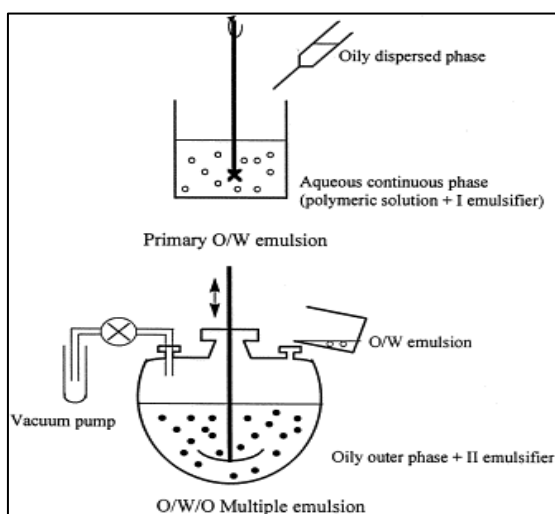
In this emulsion solvent diffusion technique, first the drug is dissolved in suitable polymer solution this drug polymer mixture is dissolved in a mixture of ethanol and dichloromethane (1:1) then the mixture is added drop wise to sodium lauryl sulphate (SLS) solution. The solution is stirred with propeller type agitator at room temperature at 150 rpm for 1 hour, washed and dried in a desiccators at room temperature. The floating microspheres prepared by this method have improved residence time in colon.

D. Emulsion Heat Stabilising Technique [28]

In this method, the emulsification of the drug is done by mixing the aqueous phase to oily phase, first 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 suitable oil and 5ml of diethyl ether with 1% span-80 (as emulsifier) and stirred it for 20 minutes 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 minutes at 800-1000 rpm. The prepared primary emulsion is added to pre-heated (65 to 70oC) oil (80 ml) by using 21 No. needle and stirred at 1000-1200 rpm for 2

hours 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 minutes 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 desiccators overnight and stored at 40°C in dark.

Fig: 7.



E. Multiple Emulsion Method [29]

Multiple emulsion method of micro sphere preparation involves the preparation of the multiple emulsion or double emulsion of type w/o/w and it is be suited to water soluble drugs, peptides, proteins and the vaccines. 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 of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization before addition to the aqueous solution of the polyvinyl alcohol, this results in the formation of double emulsion. This emulsion is then subjected to solvent removal either by solvent evaporation or solvent extraction. Shown in figure no 7

F. Co-Acervation Phase Separation Technique [30-31]

This process mainly involves in three steps under continuous stirring.

Step: 1. The core material is dispersed in a coating polymer solution.

Step: 2. The coating is accomplished by controlled physical mixing of coating solution and core material in liquid manufacturing vehicle phase.

Step: 3. Regidisation of coating polymer. This can be done by following methods.

a) Thermal method- Microspheres are formed by dissolving polymer in cyclohexane with vigorous stirring at 80 °C by heating. Then the drug is finely pulverised 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.

b) Non Solvent Addition: Microspheres are formed by dissolving polymer in toluene containing propyl-isobutylene in a closed beaker with stirring for 6 hours at 500 rpm and the drug is dispersed in it. Stirring is continued for 15 minutes, and then phase separation is brought about by petroleum benzene with continuous stirring. The microcapsules washed with n-hexane and air dried for 2 hours 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; co-acervation 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

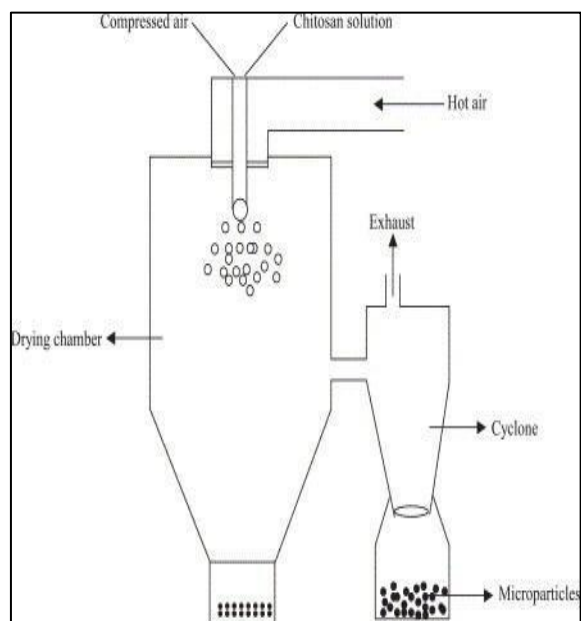
4.5 and warmed to 40- 45°C. The oppositely charged macromolecules interact at these conditions and undergo co-acervation. While maintaining the warm temperature, the liquid core

material (methyl salicylate) is added to polymer solution and stirred well. Then the mixture is cooled to 25°C and coating is rigidised by cooling the mixture to 10°C.

G. Spray drying technique [32-33]

The polymer is first dissolved in a suitable volatile organic solvent such as dichloro methane, acetone. The polymer is first dissolved in a suitable volatile organic solvent such as dichloro methane, acetone etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenisation. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporate instantaneously leading to the formation of the microspheres in a size range 1-100micrometers, thus formed microspheres are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. The major advantage of this process is feasibility of operation under aseptic condition, this process is rapid and this leads to the formation of porous microparticles as shown in figure8

Fig: 8.



H. Polymerisation Technique [34-35]:

The polymerization technique mainly involves two methods.

- (a) Normal polymerization.
- (b) Interfacial polymerization.

(a) Normal polymerization:

Normal polymerization classified as:

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

1. Bulk polymerisation: 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: it 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 the 100 micro meters.

3. Emulsion polymerization: This technique differs from the suspension and 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.

I- Ionic-Gelation Technique [36]:

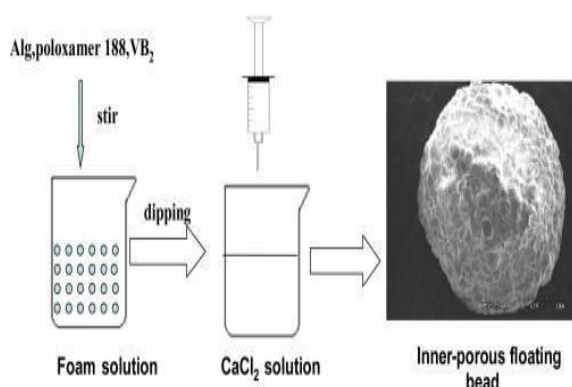
The ionotropic gelation technique is successfully used for the preparation microspheres by using low density polymers and gas generating agents like tartaric acid, citric acid etc.

In this technique low density polymer is dissolved in purified water to form a homogeneous polymer solution.

The core material or 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_2 solution through a syringe with a needle of diameter 0.55mm.

The added droplets are retained in CaCl_2 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. The floating microspheres as shown in figure-9

Fig: 9.

Hydroxyl Appetite (HAP) Microspheres in Sphere Morphology [37]:

HAP granules used in this process are obtained by precipitation method followed by spray drying process. First 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.

Hot Melt Microencapsulation Technique [38]:

In this method the polymer is first melted and then mixed with solid particles of the drug that has been sieved to less than 50 micro meters. The mixture is suspended in a non-miscible solvent like silicone oil by continuous stirring 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 micro meters 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.

Examples of Drugs Formulated as Floating Microspheres

Method	Drug	Polymer
Solvent evaporation technique	Acyclovir [39]	SCMC, HPMC
Emulsion solvent diffusion technique	Diclofenac sodium [40]	Ethyl cellulose
Ionotropic gelation technique	Diltiazem	HPMC K15, Carbapol 934
Emulsion cross linking technique	Metaprolal succinate [41]	Chitosan
Co-acervation phase separation technique	Ofloxacin [42]	Gelatin
Emulsification heat stabilising technique	Zidoverdine [43]	HPMC
Emulsion solvent evaporation technique		

Tapped Density [45]: Tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus

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

Compressibility index:

$$I = \frac{v_b - v_t}{v_b} \times 100$$

Where

v_b = bulk volume

v_t = tapped volume.

Percentage Yield [46]:

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 [35]: 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 hours until there is no change in the dried mass of sample. The swelling index of the microsphere is calculated by using the formula.

Swelling index = mass of swollen microspheres-mass of

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

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 Buoyancy (%) = $W_f / (W_f + W_s) \times 100$ Where, W_f = weight of floating micro spheres, W_s = weight of the settled microspheres. **ENTRAPMENT EFFICACY [47]:** 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. Entrapment efficiency = actual drug content / theoretical drug content. **Iso Electric Point [23]:** The ISO electric point of can be measured by using micro electrophoresis apparatus by measuring electrophoretic mobility of microspheres. The mean velocity μ 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) [21]:** The drug - polymer interaction and also degradation of drug while processing for microspheres can be determined by FTIR.

4.0 Conclusion

Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs.

The increasing sophistication of delivery technology will ensure the development of increase number of gastro retentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism.

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.

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