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FLOATING MICROSPHERES - AN EXCELLENT APPROACH FOR GASTRIC RETENTION

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ABSTRACT

Background: The gastro-retentive system is one of the promising oral drug delivery system due to its ability to remain in the gastric region for a longer period. This helps in improving the bioavailability by increasing the solubility and reducing drug wastage. **Approach:** Various approaches have been put forward to achieve the gastro-retentive property. Among them, floating (hollow) microsphere is the most prominent approach. **Findings:** Hollow microspheres are spherical free flowing powders in the size range of 1-1000 μm without core. It is prepared using proteins or synthetic polymers. This buoyant system improves gastric retention, sustains the drug release, and hence reduces the fluctuations in plasma drug concentration. **Conclusion:** This review presents an insight into recent advances in methods of fabrication, evaluation and applications of hollow microspheres as gastro-retentive drug delivery systems.

Key words: *Floating microspheres; Gastro-retentive drug delivery; Gastric retention time; Buoyancy.*

INTRODUCTION

All the drug delivery systems aim at providing adequate drug concentration at site of action and maintain the desired drug concentration.[1] A good knowledge about the physiological and biological parameter of the drug is the key parameter for developing the drug delivery system.[2] Of the various drug delivery systems, oral drug delivery system is the most preferred due to the ease of administration, better patient compliance, flexibility of formulation approaches and reduced frequency of drug administration.[3,4] Among the various market formulations, 50% of formulations are oral formulation.[5] Major difficulties of the oral drug delivery are physiological due to the failure to maintain and localize the drug delivery system within the desired region of GIT. These difficulties are due to variation in gastric emptying, leading to non-uniform absorption profile, shorter residence time of the dosage form in the stomach and insufficient drug release.[6] Gastric emptying is an extremely variable parameter. By prolonging and controlling the emptying time helps in the development of dosage forms. These considerations have led to the development of oral controlled release dosage form with gastro-retentive properties[7], which help the drug to remain in the gastric region for a longer period, increases the gastric retention time. This ultimately improves bioavailability, reduces drug wastage and improves solubility of the drug.

Gastro-retentive drug delivery:

GRDDS (Gastro-retentive drug delivery system) can remain in the gastric region for a longer time and hence significantly prolong the gastric retention time (GRT) of drugs. Various gastro-retentive drug delivery approaches in practice include high density (sinking) systems that are retained at the bottom of the stomach[8], low density (floating systems, that causes buoyancy in gastric fluid) [9,10], mucoadhesive systems (causes bio-adhesion to stomach mucosa)[11], unfoldable, extendible, or swellable systems that limit emptying of the dosage forms through the pyloric sphincter of stomach[12,13], super porous hydrogel systems[14], and magnetic systems[15]etc.

Factors affecting Gastro-retentive drug delivery

- Density: Density is an important parameter for gastric emptying time and also determines the buoyancy of dosage form; a density of < 1.0 gm/cm^3 is ideal for exhibiting good floating property.[17]
- Size: The mean residence time of floating and non floating dosage form depends on the size of the dosage form. To pass the dosage form from the pylorus to intestine, it should be in the range of 1 to 2 mm. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. The larger size of the dosage form would not allow quick passage through the pyloric antrum into the intestine.[17]
- Shape of dosage form: Shape is an important parameter to design a single unit dosage form, tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better gastric retention time up to 24 h compared to other shapes.[17]
- Single or multiple unit formulation: Multiple unit formulation can overcome the drawback of single unit formulation like sticky nature, obstruction in gastrointestinal tract and irritation. Therefore, multiple unit formulation shows a more predictable release profile.[18,19]
- Fed or unfed state (under fasting conditions): The presence and absence of food affects the gastric retention time, usually the fed state improves the gastric retention time and

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increases the absorption of the drug by prolonging the drug to remain at the absorption site. In the fasting condition, the GI motility is characterized by strong motor activity (Fig.1), which pushes the undigested material from stomach to intestine and hence GRT of the unit is very short.[20-22]

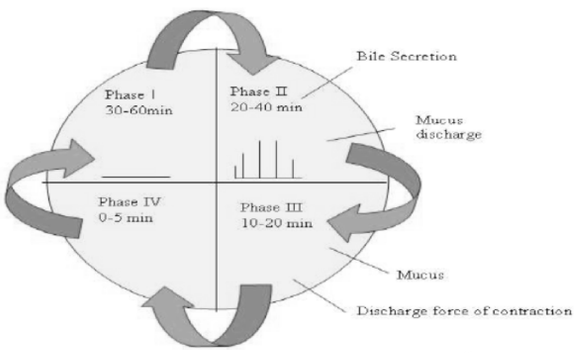

Fig.1: *Motility patterns of the GIT in the fasted state*[16]

[Reproduced from:Guyton AC. Movement of food through the alimentary tract. in: human physiology and mechanisms of disease, London: W.B. Saunders Co;1982, 3, 487-497.]

- Nature and caloric content of meal: Food contains indigestible polymers or fatty acid salts can change the motility pattern of the stomach, resulting in decreased gastric emptying rate and thus prolongs drug release. High caloric meals, such as proteins and fats increase the GRT from 4 to 10 h.[20-22]
- Frequency of feed: Successive meals in comparison to single meal, increases the GRT over 400 min.[20-22]
- Effect of gender, age and posture: Mean ambulatory GRT in females is less compared to male and hence gastric emptying time in female is less than that of males. Elderly people above the age of seventy have longer gastro-retention time. The effect of posture on the GRT is found to produce no significant difference in the upright and supine position.[23,24]
- Concomitant drug administration: Anticholinergics such as atropine, propantheline and opiates such as codeine increases the gastric retention, whereas prokinetic agents like metoclopramide and cisapride decreases the gastric retention.[25]
- **Physiological factors**

  ***Mechanism of absorption*:**

  Orally administered drugs are absorbed both by passive diffusion as well as by non passive way of absorption. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity due to the prevalence of these mechanisms only in a particular region of gastro intestinal tract.[26]

  Metabolic Enzymes:

  Presence of certain enzymes in specific location in G.I. tract can also lead to regional variability in absorption. Intestinal epithelium consists of phase I metabolizing enzymes, such as cytochrome P450 in abundance, their activity decreases longitudinally along the small intestine, and their levels increasing from duodenum to the jejunum and then declining in the ileum and colon. This non-uniform distribution of cytochrome P450 causes regional variability in the absorption of drugs that are substrate to these enzymes.[27]

Drugs suitable for designing gastro-retentive dosage form[17]

1. Drugs those are locally active in the stomach e.g., misoprostol and antacid.
2. Drugs that have narrow absorption window in the gastro intestinal tract. e.g., riboflavin and levodopa.
3. Drugs absorbed primarily from the stomach and upper part of the stomach e.g., Calcium supplements and chlordiazepoxide.
4. Drugs that degrade in the colon e.g., ranitidine HCl and metronidazole
5. Drugs that disturb the normal colonic bacteria. E.g., amoxicillin trihydrate.
6. Drugs that exhibit low solubility at high pH values e.g., diazepam, chlordiazepoxide, and verapamil HCl.

Advantages of Gastro-retentive Drug Delivery Systems[17]

Improved bioavailability

The bioavailability of therapeutic agent can be significantly enhanced in case of drugs that are metabolized in the upper GIT which is given by gastro retentive drug delivery approach than non gastro retentive drug delivery approach. The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations.

Sustained drug delivery system

Gastro-retentive drug delivery can assure a prolonged local therapy in the stomach and small intestine. The sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics, which can be used to reduce dosing frequency. This results in improved patient compliance, and improves the therapy.

The controlled, slow delivery of drug form gastro-retentive dosage form provides sufficient local action at the disease site, which can minimize side effects of systemic therapy. This site-specific drug delivery reduces undesirable effects or side effects.

Reduced fluctuations of drug concentration

Gastro-retentive dosage forms minimize the variation in concentration dependent adverse effects that are associated with peak plasma concentrations, especially in case of drugs with narrow therapeutic indices. Reduced activity results in improved selectivity for activating the receptors.

Reduced counter-activity of the body

Gastro-retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes drug concentration in colon. Thus, undesirable activities of the drug in colon may be prevented. This provides the rationale for GRDF formulation of drugs such as beta-lactam antibiotics, which gets absorbed only from small intestine and whose presence in the colon leads to the development of microorganism's resistance.

Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides limited systemic side effects, sufficient local therapeutic levels. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

Limitations of Gastroretentive Drug Delivery Systems[28]

1. Gastro retentive dosage form is not suitable for those drugs that have solubility or stability problem in the stomach.
2. Drugs which are well absorbed along the entire gastro intestine tract and which undergo significant first pass metabolism e.g., nifedipine.
3. Gastro-retentive system requires high fluid level in the stomach for drug delivery system to float and work efficiently.
4. Drugs which are gastric irritant are also not suitable.
5. These systems are not suitable for the conventional dosage forms for those drugs, which are absorbed throughout the intestinal tract.

FLOATING DRUG DELIVERY SYSTEMS[29]

Floating Drug Delivery Systems (FDDS) have bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, (Fig. 2) without affecting the gastric emptying rate. From such systems, drug is released at a desired slower rate and also residual system can be emptied from the stomach. This results in an augmented GRT and a control over fluctuations in the plasma drug concentrations.

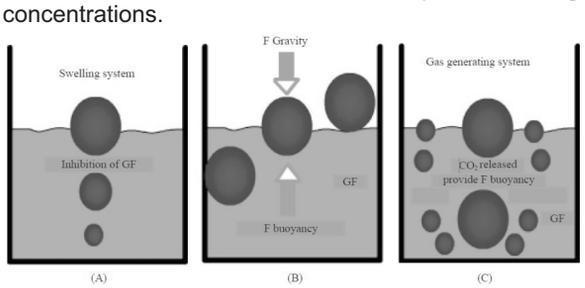

Fig. 2: *Mechanism of floating systems: (A) Swelling system (B) Buoyant systems (C) Gas generating system*

[Reproduced from: Arrora S, Ali J, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS Pharm Sci.Tech. 2005; 6(3):372-90.]

***Mechanism of drug release*:**

The mechanism of drug release from multi-particulate system is as follows:

Diffusion: Drug diffusion is initiated by uptake of gastrointestinal fluids to the interior of the drug delivery system, followed by dissolution of the drug and slow release from the delivery system to the exterior by diffusion mechanism.

Erosion: Coatings around the drug particles can erode slowly, there by the drug action may be sustained.

Osmosis: Uptake of water within the drug delivery system builds up osmotic pressure, by suitable means, which pushes the drug out of delivery system in a sustained manner.

Components of floating drug delivery system[30]

The components used in floating technology and their uses are mentioned in Table 1 and examples of polymers and their applications are mentioned in Table 2

Table 1: *Ingredients used in floating drug delivery system* [30]

Ingredients	Subtype	Example
Polymer	Natural polymers	***Proteins***: Albumin, Gelatin, Collagen. ***Carbohydrates***: Agarose, Carragenan, Chitosan, Starch. **Chemically modified carbohydrates**: Poly dextrans, Poly starch.
	Synthetic polymers	***Biodegradable***: Lactides, glycolides, their co polymers, Polyalkyl cyanoacrylates, Polyanhydrides. ***Non Biodegradable***: Polymethyl methacrylate, Acrolin, Glycidyl methacrylate, Epoxy polymers.
Other Ingredients	Inert fatty material (they have less specific gravity and hence increases the hydrophilic character, thereby increases the buoyancy)	Beeswax, fatty acid, long chain fatty alcohols.
	Effervescent agent	Sodium bicarbonate, citric acid, tartaric acid, disodium glycine carbonate(Di-SGC), Citroglyine.
	Release rate accelerants	Mannitol, lactose.
	Release rate retardant	Dicalcium phosphate, talc, magnesium stearate
	Buoyant increasing agent	Ethyl cellulose.
	Low density material	Polypropylene foam powder.

Table 2: *Polymers and applications*[31-34]

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
Polyvinyl alcohol, Polyacrlydine	Adsorption of harmful substance in blood.

Method of Preparation

The following methods are used for preparation of floating microparticulate drug delivery system.

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. Coacervation 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. Polymerization technique
   a) Normal polymerization
   b) Interfacial polymerization
I. Ionic gelation technique
J. Hydroxyl appetite (HAP) microspheres in sphere morphology
K. Hot melt microencapsulation technique

Emulsion solvent evaporation technique[35-36]

The coating polymer is dissolved in an organic solvent which is immiscible with the liquid manufacturing vehicle. A core material (water soluble or water insoluble materials) is dissolved or dispersed in the coating phase with agitation. The above solution 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, polymer shrink around the core and the process is depicted in Figure 3. If the core material is dissolved in the coating polymer solution, matrix type microcapsules will be formed.

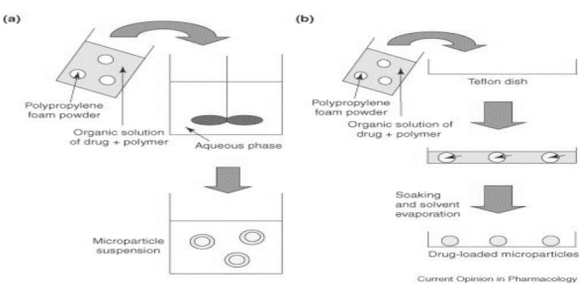

Fig. 3: *Emulsion Solvent Evaporation Technique*

[Reproduced from: Kavita K, Ashvini VR, Ganesh NS. Albumin microspheres. Unique system as drug delivery carriers for non steroidal anti inflammatory drugs. Int. J. Pharm. Sci. Rev. & Res. 2010; 5(2):10.]

Emulsion cross linking technique[37]

This method is used for microparticles of natural carriers. The natural polymers are dissolved or dispersed in aqueous medium followed by addition of non-aqueous medium. The drug is dissolved in aqueous solution of carrier such as gelatin which is previously heated for 1hr at 40ºC. The resultant solution is added drop wise to oil phase such as liquid paraffin containing a suitable surfactant at a stirring speed of 1500 rpm for 10 min at 3ºC. This resultant w/o emulsion is further stirred for 10 min at 15ºC. The microspheres are washed with suitable organic solvents such as acetone and isopropyl alcohol, and air dried. The formed microspheres are cross linked by dispersing in 5 ml of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs, further treated with 100 ml of 10 mM glycine solution containing 0.1% w/v of tween 80 at 37ºC for 10 min to stop the cross linking. 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 stabilize the emulsion phase can greatly influences the size, size distribution, surface morphology, loading, drug release and biological performance of the final multi-particulate product.

Emulsion-solvent diffusion technique[38]

In this method, first the drug is dissolved in suitable polymer solution in ethanol and dichloromethane. This drug polymer solution is added drop wise to sodium lauryl sulphate (SLS) solution, stirred by propeller type agitator at room temperature at 150 rpm for 1 h, washed and dried in desiccator at room temperature. The flow diagram is represented in Figure 4. The floating microspheres prepared by this method have improved residence time in colon.

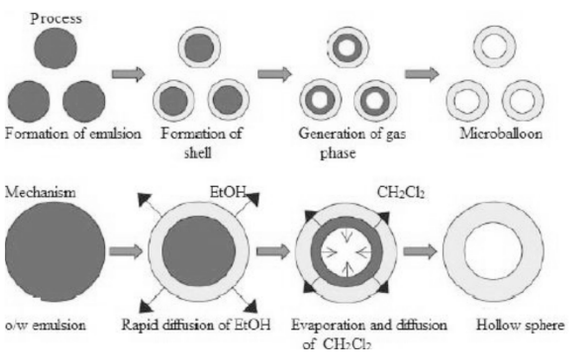

Fig. 4: *Emulsion- Solvent Diffusion Technique*

[Reproduced from: Phalguna Y et al. HPMC Microspheres of zidovudine for sustained release. Inter. J. of Pharm. and Pharmaceut. Sci. 2010; 2(4): 41-43.]

Emulsion heat stabilizing technique[39]

The aqueous polymer solution is prepared by dissolving polymer (egg albumin) in water in presence of surfactant such as Tween 80 by mechanical stirring, for 30 min. Similarly, the oil phase is prepared by mixing 20 ml of suitable oil and 5ml of diethyl ether with 1% span 80 (as emulsifier) by magnetic stirring. Further oil phase is added to aqueous phase by stirring at 800-1000 rpm for 30 min. The above primary emulsion is added to pre-heated (65 to 70ºC) oil by passing through the needle (No:21) and stirred at 1000-1200 rpm for 2 h till the solidification of microspheres takes place. The resulted microsphere suspension is cooled to room temperature by magnetic stirring; 100 ml of anhydrous ether is added. The above suspension is centrifuged for 15 min, washed with ether to remove oily trace. The obtained microspheres are then dried in vacuum desiccators overnight and stored at 4ºC in dark.

Multiple emulsion method[40]

This method is suitable for water soluble drugs such as proteins and peptides. The primary emulsion, o/w type is prepared by dissolving drug in aqueous protein solution containing an emulsifier. The dispersed phase containing lipophilic organic phase, is added to it. (Fig 5). The primary emulsion obtained is then subjected homogenization followed by addition to the aqueous solution of polyvinyl alcohol, which results in the formation of double emulsion. This is then subjected to solvent evaporation or solvent extraction.

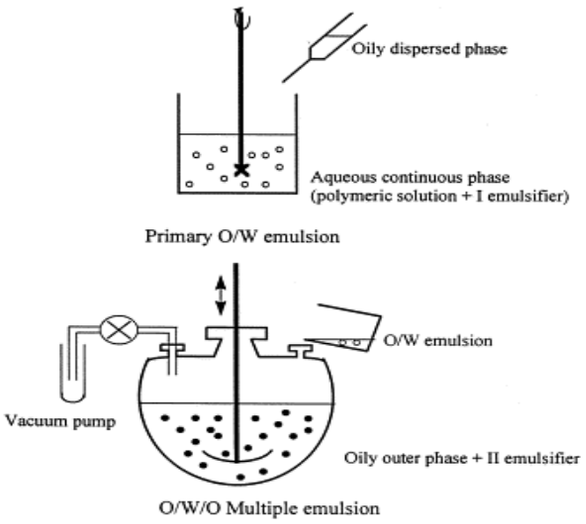

Fig. 5: *Multiple Emulsion Method*

[Reproduced from: Patel G, Tiwari A, Rabadia N. Floating microspheres as novel tool for H_2 receptor blocker. IRJP, 2012; 3(2): 45-52.]

Coacervation phase separation technique[41-42]

This process mainly involves following steps

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**:** Rigidisation of coating polymer by following methods.

a) *Thermal Change*

Polymer is dissolved in cyclohexane by vigorous stirring at 80ºC, drug is added to the above solution with constant stirring. The microsphere is obtained reducing temperature by keeping in the ice bath. The product is washed twice with cyclohexane and air dried.

b) *Non Solvent Addition*

Initially, polymer is dissolved in toluene containing propyl isobutylene in a closed beaker with stirring for 6 h at 500 rpm and the drug is dispersed in it. The resulted solution is added to benzene with continuous stirring. The microcapsules are washed with n-hexane and air dried for 2 h.

c) *Polymer Addition*

Microspheres are formed by dissolving polymer (ethyl cellulose) in toluene, methylene blue is added as core material. Coacervation is accomplished by the addition of liquid polybutadiene. Polymer coating is solidified by adding a nonsolvent (hexane). The resulting product is washed and air dried.

d) *Salt Addition*

Oil soluble vitamin is dissolved in corn oil and is added to gelatin solution at 50ºC. Coacervation is induced by adding sodium sulphate, which results in uniform coating of gelatin. The microspheres are collected and washed, chilled and dried .

e) *Polymer-Polymer Interaction*

In this process, homogeneous polymer solution is obtained by mixing aqueous solution of gum Arabica and gelatin (isoelectric point 8.9) in equal amounts. The above solution is diluted twice their volume with water, adjusted to pH 4.5 and warmed to 40-45ºC. The oppositely charged macromolecules interact at these conditions and undergo coacervation. While maintaining the warm temperature, the liquid core material is added to polymer solution and stirred well. Then the mixture is cooled to 25ºC and coating is rigidised by cooling the mixture to 10ºC.

Spray drying technique[43,44]

The polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. The drug is added to the polymer solution under high speed homogenization. Atomization of the above dispersion in a stream of hot air, leads to the formation of small droplets or the fine mist. Solvent gets evaporated instantaneously leading to the formation of the microspheres of size range 1-100 µm. Microspheres are separated from the hot air by means of the cyclone separator The major advantage of this process is feasibility of operation under aseptic condition, rapid and leads to the formation of porous microparticles, which can be used for poorly soluble drugs. The entire process is presented in Figure 6.

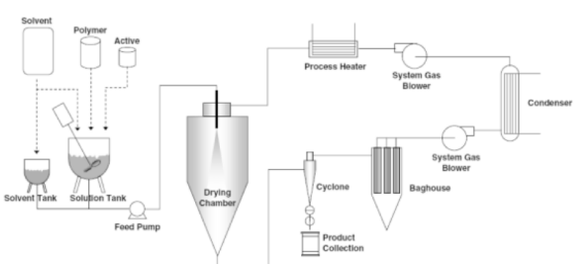

Fig. 6: *Spray drying technique*

[Reproduced from: Rajput GC, Majmudar DF, Patel KJ, Patel NK, Thakor SR, Patel RR, et al. Floating drug delivery system- A review. Pharm. Ext. 2010; 1(1) 43-5.]

Polymerization technique[44,45]

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

Bulk polymerization

Polymerization is initiated by heating a monomer or a mixture of monomers along with the initiator or catalyst, drug is loaded simultaneously. Though it is a simple technique, it cannot be applied for the thermo labile active ingredients.

Suspension polymerization

In this pearl polymerization method, monomer mixture is heated at lower temperatures than polymerization, with

active drug as droplet dispersion in continuous aqueous phase. Particle size microspheres are usually less than 100 micro meters.

Emulsion polymerization**:** This technique is carried out in presence of initiator in aqueous phase at low temperature as suspension. External phase normally water 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.

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.

***Ionic gelation technique*[46]**

This technique is successfully used for the preparation microspheres by low density polymers and gas generating agents such as tartaric acid, citric acid etc. Aqueous homogeneous polymer solution is prepared by dissolving polymer in water. The core material which is finely sieved (sieve 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 0.55 mm as presented in Figure 7. Curing is done by stirring at 200 rpm for 15 min which results in spherical rigid microsphere. Finally the microspheres are collected and dried in an oven at a temperature 45ºC for 12 h.

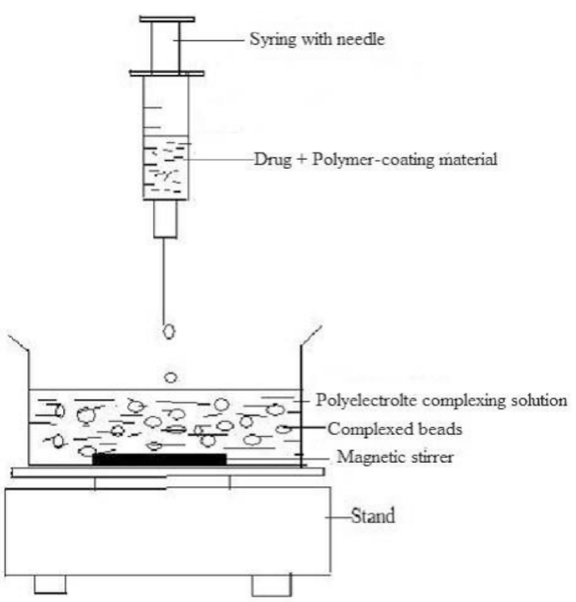

Fig. 7: *Ionic-Gelation Technique*

[Reproduced from: Tirupati M. et al., Comparative Study of ionotropic gelation technique to entrap diltiazem HCl in mucoadhesive microparticulate system. J. of Pharma. Res. 2010; 3(7):1531-1534.]

***Hydroxyl appetite (HAP) microspheres in sphere morphology*[47]**

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 Ethylene vinyl acetate 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 solidify 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*[48]**

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 till the solidification of solid particles. The resulting microspheres are washed by decantation with petroleum ether. This method is suitable for the water labile polymers, e.g. polyanhydrides. Microspheres with diameter of 1-1000 µm can be obtained. Particle size can be altered by changing the stirring speed. The only disadvantage of this method is moderate temperature to which the drug is exposed.

EVALUATION OF FLOATING MICROPARTICULATE DRUG DELIVERY

Micromeritics[49]

Microspheres are characterized for their micromeritics properties such as particle size, angle of repose, compressibility index and Hausner ratio.

Particle size[49]

The particle size of the microspheres is measured using an optical microscopy and mean size is calculated by measuring 200-300 particles with the help of a calibrated ocular micrometer.

Bulk density[50]

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10 gm sample of microsphere is placed into 25 ml measuring cylinder. Volume occupied by the microsphere is noted without disturbing the cylinder and the bulk density was calculated using the equation (expressed in gm/cm^3).

$$\text{Bulk density} = \frac{\text{Weight of microspheres}}{\text{Bulk volume}}$$

Tapped density[50]

Tapping method is used for the determination of tapped density. In this method, 10 gm of hollow microsphere sample is placed in 25 ml measuring cylinder and dropped at a height of one inch onto a hard wooden surface 100 times at a interval of 2 seconds. The final volume was recorded and the tapped density is calculated by the following equation (expressed in gm/cm^3).

$$\text{Tapped density} = \frac{\text{Weight of microspheres}}{\text{Tapped volume}}$$

Carr's index[51]

The Carr's index indicates of the flowability and compressibility of a powder. This is calculated from the values of bulk density and tapped density by using the formula:

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

Carr's index greater than 25% indicates of poor flowability and below 15% of good flowability. The relationship between Carr's index and flow property is represented in Table 3.

Table 3: *Carr's index as an indication of powder flow*

Carr's index	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner ratio[51]

The Hausner ratio indicates the compressibility and flow property of a powder. This is calculated from the values of bulk density and tapped density by using the formula:

Hausner ratio = [Tapped density / Bulk density]

A Hausner ratio greater than 1.25 is an indication of poor flowability.

Angle of repose[51,52]

The angle of repose is indicative of flowability of the substance. This can be determined by funnel method. The height of the funnel is adjusted in such a way that stem is 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel adjusted at a height of 2.5 cm from the stem. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters. It is calculated by the formula

$$\text{Angle of repose } (\theta) = \tan^{-1} (h/r)$$

Where, θ is angle of repose, h is height of the pile; r is the radius of the pile.

The relationship between the angle of repose and flowability is given in Table 4.

Table 4: *Relationship between angle of repose (θ) and flowability*

Angle of Repose	(θ)Flowability
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

Percentage yield[53]

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:

$$\text{\% yield} = \frac{\text{actual weight of product}}{\text{total weight of drug and excipients}} \times 100$$

Morphological Study using SEM:[53]

The external and internal morphology of the microspheres is studied by using scanning electron microscopy (SEM).

FT-IR (Fourier Transform Infra Red):[54]

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

Drug entrapment efficiency (DEE)[55]

The amount of drug entrapped is estimated by crushing the microspheres and extracting with suitable solvent repeatedly. The extract is filtered and the absorbance is measured by spectrophotometer. The amount of drug entrapped in the microspheres is calculated by the following formula:

$$\text{DEE} = \frac{\text{Total drug - free drug}}{\text{Total drug}} \times 100$$

***In vitro* Buoyancy**[56]

Floating microspheres should be placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture is stirred at 100 rpm with a magnetic stirrer. After 8 h, the layer of buoyant microspheres is pipetted and separated by filtration. Particles in the sinking particulate layer are separated by filtration. Particles of both types are dried in a desiccators until constant weight is achieved. Both the fractions of microspheres are weighed and buoyancy is determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{\% buoyancy of microspheres} = \frac{\text{weight of floating microshperes}}{\text{initial weight of floating Microspheres}} \times 100$$

Dissolution test (*in vitro* drug release) of microspheres[57]

In vitro dissolution studies can be carried out in a USP paddle type dissolution assembly. Drug dose equivalent microspheres are added to 900 ml of the dissolution medium and stirred at 100 rpm at 37 ± 0.5 ºC. Samples are withdrawn at a specified time interval and analyzed by any suitable analytical method, such as UV spectroscopy.

Thermal Analysis[58]

Thermal analysis of microspheres and its component can be done by using (DSC), Thermo Gravimetric Analysis (TGA) and Differential Thermometric Analysis (DTA). Accurately the sample was weighed and heated on alumina pan at constant rate of 10°C/min under nitrogen flow of 40 ml/min.

Floating Studies[59]

This test is to determine the floating time of the system, performed in simulated gastric fluid or 0.1 M HCl maintained at 37°C, by using USP dissolution apparatus. The time taken by the dosage form to float is termed as floating lag time and time for which the dosage form floats is termed as floating time.

Swelling Studies[59]

Swelling studies were performed to calculate molecular parameter of the swollen polymers. Swelling studies was determined by using, dissolution apparatus, optical microscopy, H1NMR imaging, Confocal Laser Scanning, and Light Scattering Imaging.

The swelling studies by dissolution apparatus was calculated by the formula:

$$\text{Swelling ratio} = \frac{\text{Weight of wet formulation}}{\text{Weight of the formulation}}$$

Stability Studies[60]

Optimized formulation was sealed in aluminum packaging, coated inside with polyethylene. The samples were kept in the stability chamber maintained at 40 ± 2ºC and 75% ± 5 % RH for 3 months. At the end of studies, samples were analyzed for the physical appearance and drug content.

APPLICATION OF FLOATING MICROPARTICULATE DRUG DELIVERY SYSTEM[61]

Sustained Drug Delivery

Floating microparticulate of non-steroidal anti-inflammatory drugs is very effective for controlled release as well as it reduces the major side effect of gastric irritation. For example, floating microspheres of Indomethacin are quiet beneficial for rheumatic patients.

Solubility Enhancement

Floating microparticulates are especially effective in delivery of sparingly soluble and insoluble drugs. As solubility of a drug decreases, dissolution time becomes insufficient and thus the transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The sited gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.

As carriers

The floating microiparticulates can be used as carriers for drugs through the absorption windows (for example: antiviral, antifungal and antibiotic agents such as sulphonamides,quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) are taken up only from very specific sites of the gastro intestinal mucosa.

Site-Specific Drug Delivery

Floating microparticulates can greatly improve the pharmacotherapy of the drug in the stomach through local drug release, leading to high drug concentrations at the gastric mucosa. Eg: Floating drug delivery system can eradicate *Helicobacter pylori* from the sub mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.

Pharmacokinetic advantages and future potential

It is evident from recent researches that floating dosage form offers potential advantages as that of sustained release system**.** Drugs that have poor bioavailability because their absorption is restricted to the upper GI tract can be delivered efficiently there by maximizing their absorption and improving their absolute bioavailability. Gastroretentive dosage form available in market are given in Table 5.

Table 5: *Marketed Products of GRDFs:*

Brand name	Delivery system	Drug	Company name
Cifran OD®	Gas-generating floating form	Ciprofloxacin	Ranbaxy, India
Convoron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol	Pharmacia, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide, Mg carbonate	Glaxosmithkline, India
Madopar ®HBS (Prolopa®HBS)	Floating, CR capsule	Benserazide and L-Dopa	Roche Products, USA
Oflin OD®	Gas generating floating tablet	Ofloxacin	Ranbaxy, India
Topalkan®	Floating liquid alginate preparation	Al-Mg antacid	Pierre FabreDrug, france
Valrelease®	Floating capsule	Diazepam	Hoffmann-LaRoche, USA

CONCLUSION

Gastrointestinal absorption of drugs is highly unpredictable process. Floating microsphere is a potential approach for gastric retention, which results in a site specific, controlled drug release, and has an enormous impact on health care. These systems also provide tremendous opportunities in designing novel oral formulations, thus extending the frontier of futuristic pharmaceutical development. Furthermore, latest novelties in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

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