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Review Article

Floating Microspheres: A Novel Drug Delivery System

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ABSTRACT

The motivation behind composing this audit on Floating microspheres is to gather the ongoing writing with unique spotlight on the essential system of buoyancy to accomplish gastric maintenance. Floating microsphere pledges to be a potential philosophy for gastric retention. The floating microspheres have been created trying to discharge the medication gradually into the GIT and keep up a compelling medication fixation in the serum for longer timeframe. From the system and technological factor of view, the floating drug delivery system is comparatively clean and logical approach. In this review, the current status of floating microspheres including hollow microspheres (micro balloons) and their characterization, advantages disadvantages, application, mechanism and method of preparation for gastric retention of drug are discussed. This review additionally summarizes the *in vitro* and *in vivo* studies to evaluate the overall performance and programs of floating microspheres.

INTRODUCTION

The layout of oral managed drug delivery device have to in the main be geared toward achieving extra predictable and multiplied bioavailability of drug [1]. Thus the purpose of drug delivery gadget is to offer a therapeutic quantity of drug to the proper site within the frame to achieve promptly & then preserve the favored drug concentration. Drug which can be without difficulty absorbed from the GIT and having a brief half-life are eliminated fast from the blood circulation.To avoid these issues oral managed drug delivery structure were advanced as they releases the drug slowly into the GIT and maintain a regular drug concentration in the serum for longer duration of time [2]. It has been often determined that the drug that are easily absorbed form GI tract have a short half live and are eliminated quick from the systemic flow which result in incomplete of drug from upper a part of small intestine [3]. Recent clinical and patent literature has shown increased interest in novel dosage bureaucracy that can be retained in the stomach for a extended and predictable duration of time. GRDF are designed on the idea of one of the several procedures like formulating low density dosage shape that stay buoyant above the gastric fluid (FDDS) or excessive density dosage shape that is retained at the bottom of the belly, imparting bio-adhesion to the stomach mucosa, reducing motility of the GIT by means of concomitant administration of medicine or pharmaceutical excipients, expanding the dosage shape via swelling or unfolding to a huge size which limits the emptying of the dosage form via the polymeric sphincter, making use of ion-alternate resin which adheres to mucosa, or using a modified shape system [4, 5].

Physiology Consideration:

The belly is situated in the left upper part of abdominal cavity immediately under the diaphragm. Its size fluctuates in understanding to the measure of distension: as much as 1500 ml following a dinner; after nourishment has purged a fallen nation is gotten with resting amount of 25-50 mL. Anatomically the belly is split into three regions: fundus, frame and antrum (pylorus) [4, 6]. The proximal part manufactured from fundus and frame acts as a reservoir for undigested material, the antrum is

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the principle website for blending motions and act as a pump for gastric emptying via propelling actions (Desai, 1984) [7].

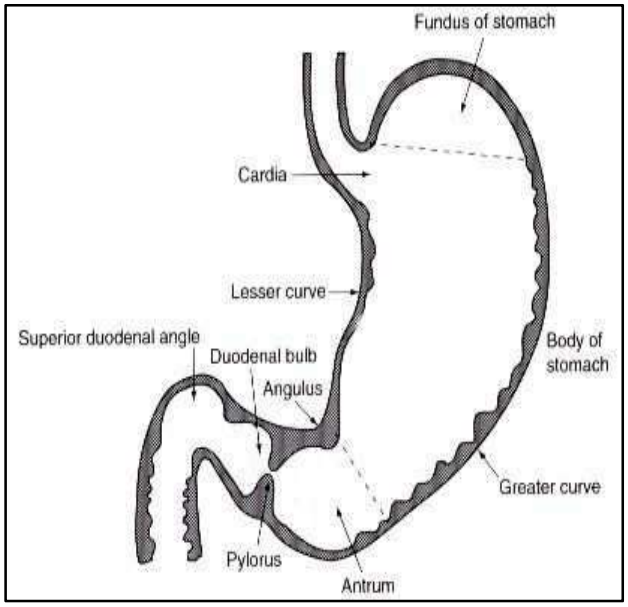

Figure 1: Anatomy of stomach.

Drugs having a short half-lifestyles are eliminated quick from the blood circulate and therefore bioavailability of the drug suffers. Gastro retentive dosage form improves bioavailability, healing efficacy and may permit a reduction within the dose due to regular healing degrees of drug, for example furosemide and ofloxacin [8]. Gastric emptying takes place in the course of fasting as well as fed states, however the pattern of motility is distinct within the two states. During the fasting kingdom an interdigestive series of electrical events take place, which cycle both through stomach and intestine each 2 to a few hours. This is referred to as the interdigestive myloelectric cycle or (MMC) Migrating Myloelectric Cycle which is similarly divided into following 4 phases as described with the aid of Wilson and Washington [9]. MMC is frequently divided into 4 consecutive stages: basal (Phase I), pre-burst (Phase II), burst (Phase III), and Phase IV intervals [4].

Phase I (Basal phase): lasts from forty to 60 minutes with uncommon contractions.

Phase II (Preburst phase): lasts for 40 to 60 mins with intermittent action potential and contractions. As the segment progresses the depth and frequency will also increase gradually.

Phase III (Burst segment): Lasts for 4-6 min. It includes intense and ordinary contractions for brief periods, due to this contraction all the undigested fabric is swept out of the stomach right down to the small intestine. This is also known as the housekeeper wave.

Phase IV: remaining for 0-5 mins and occurs between section 2 and 1 of two consecutive cycles.

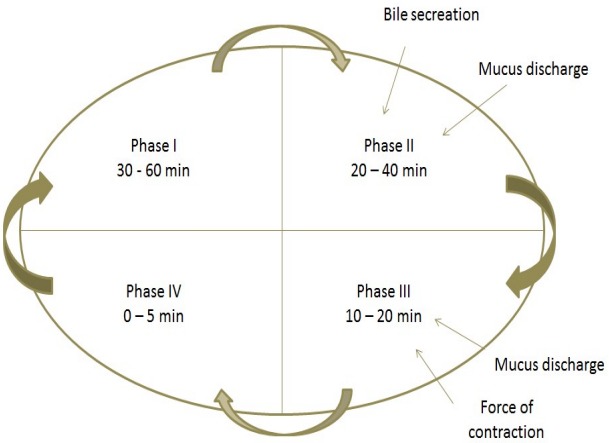

Figure 2: InterdigestiveMyloelectric Cycle or Migrating Myloelectric Cycle (MMC).

Advantage of FDDS [10-12]:

1. Improved drug absorption, because of multiplied gastric house time and more time spent through the dosage form at its absorption site .
2. Controlled shipping of drugs.
3. Delivery of drug for neighborhood motion in stomach.
4. Minimizing the mucosal irritation due to drugs, through drug freeing slowly at controlled rate.
5. Ease of management and better affected person compliance.
6. Site-precise drug delivery.
7. Masking of odour or sour taste.
8. Improve physical stability and gastric enzyme stability.
9. Reduced dose size.
10. First skip metabolism is avoided.

DISADVANTAGES OF FDDS [10-12]:

1. Rate of controlled release dosage shape may additionally vary due to certain elements like intrinsic and extrinsic factors.
2. There is difference in the price of launch of drug from one dosage from to any other dosage form.
3. Dumping of dose bring about failure of therapy.

4. Floating systems aren't viable for those drugs that have solubility or stability troubles in gastric fluids.
5. Gastric retention is influenced by way of many elements inclusive of gastric motility, pH and presence of food. These elements are in never consistent and consequently the buoyancy cannot be predicted.
6. Drugs that motive infection and lesion to gastric mucosa aren't appropriate to be prepared as floating drug shipping systems.

Factor Affecting Gastric Retention:

1. **Nature of Meal & Frequency of Food:** The larger the bulk of meal, longer will be the gastric emptying time. Diet rich in protein and fat can increase GRT by 4-10 hours [11, 13].

2. **Density**: GRT is a function of dosage form buoyancy that is depending on density [14].

3. **Effect of Dosage Form, Size & Shape:** Dosage shape gadgets with diameter of more than 7.5mm suggested to have an improved GRT in comparison with the ones of 9.9mm diameter. Tetrahedron and ring shaped gadgets with a flexi burl modulus of 48 and22.5 kilo kilos per rectangular inch are suggested to have better [11, 14].

4. **Single and Multiple Unit Formulation:** Multiple unit formulation show predictable release profile compare to single unit dosage form as single unit formulation may have chance of performance failure [14].

5. **Gender, Posture & Age:** GRT in men is less compare with their age and race matched counterparts regardless of weight, height and body surface. Their age and race matched counterparts regardless of weight, height and body surface.

6. **Diseased State:** State of the stomach also affect the environment for the dosage form as in case of ulcers, flatulence and spasms (Brahmankar and Jaiswai, 2006) [13].

7. **Drug Therapy:** It additionally performs an vital role in gastric emptying e.g. Prokinetic pills like cisapride and mosapride increase gastric emptying time whereas imipramine and atropine retards it [13].

Factors to Be Considered During Formulation [8]:

1. **Addition of Polymer Solution:** As reported that, the excessive floor tension of water induced the solidification and aggregation of polymer on the surface of aqueous section. To minimize the contact of polymer answer with the air-water interface and to expand a continuous method for making ready microspheres, a new method of introducing the polymer answer into aqueous section turned into developed. The approach involves the use of a pitcher tube immersed in an aqueous section and the creation of the polymer solution through the glass tube without contacting the surface of water. This technique progressed the yield of microspheres and decreased the extent of combination formation. As the polymer answer is continuously delivered into the principle vessel, it's going to overflow from the top of the vessel together with the organized microspheres, since maximum of the shaped microspheres will glide on the top of the aqueous phase. The microspheres, which overflow from the pinnacle of the vessel, maybe collected in a box with the precise sieve length at the bottom.

2. **Effect of Rotation Velocity**: It is obvious that the rotation velocity of propeller influences yield and size distribution of microspheres. As the rotation speed of propeller is increased, the average particle size decreases, while maintaining its morphology.

3. **Effect of Temperature:** The temperature of the dispersing medium is an important parameter in the preparation of microspheres as it controls the evaporation rate of the solvents. At lower temperature (10°C), prepared microsphere has crushed and irregularly shaped morphology. The shell of the microsphere turns translucent during the process, due to the slower diffusion rate of ethanol and dichloromethane. At higher temperatures (40°C), the shell of the microsphere becomes thin and it might be

due to faster diffusion of alcohol in the droplet into aqueous phase and evaporation of dichloromethane immediately after introducing it into the medium.

Mechanism of Floating Systems [15, 16]:

Floating drug shipping systems (FDDS) have a bulk density less than gastric fluids and so stay buoyant inside the stomach without affecting the gastric emptying charge for a prolonged length of time. While the device is floating at the gastric contents (Fig. 1), the drug is launched slowly at the desired rate from the machine. After release of drug, the residual system is emptied from the stomach. This results in an extended GRT and a superior control of the variances in plasma sedate focus. Be that as it may, aside from a negligible gastric substance expected to permit the correct accomplishment of the lightness maintenance standard, a minimum stage of floating pressure (F) is also required to hold the dosage shape reliably buoyant on the surface of the meal. To measure the floating pressure kinetics, a unique equipment for dedication of resultant weight has been reported in the literature. The equipment operates via measuring constantly the force equipment to F (as a function of time) this is required to preserve the submerged object. The object floats higher if F is on the higher positive side [Fig. 3(b)]. This apparatus enables in optimizing FDDS with respect to balance and durability of floating forces produced so as to save you the drawbacks of unforeseeable intra gastric buoyancy Capability variations.

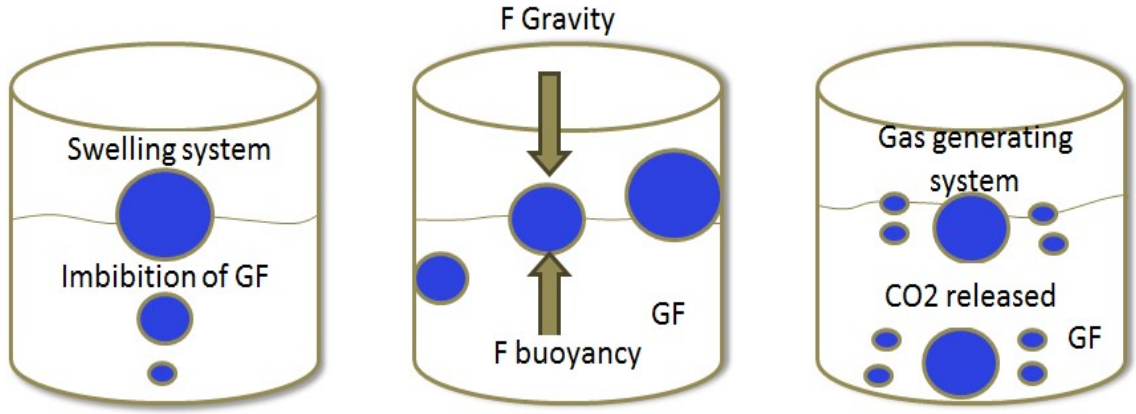

Figure 3: Different mechanisms of floating systems

F = F buoyancy - F gravity = (Df - Ds) g v ……. (1)

Where,
F= total vertical force,
Df = fluid density,
Ds = object density,
v = volume and
g = acceleration due to gravity.

Polymers and Other Ingredients [16]:

Following types of Ingredients can be incorporated into HBS dosage form in addition to the drugs:

1. **Hydrocolloids (20%-75%):** They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg. Acacia, pectin, Chitosan, agar, casein, bentonite, veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, HPC.
2. **Inert fatty materials (5%-75%):** Edible, inert fatty substances having a particular gravity of less than one may be used to lower the hydrophilic assets of formulation and hence growth buoyancy. E.g. Beeswax, fatty acids, lengthy chain fatty alcohols.
3. **Bubbly agents:** NaHCO3, citric acid, tartaric acid, Di-Sodium Glycine Carbonate, Citroglycine, calcium carbonate.
4. **Release rate accelerants (5%-60%):** e.g. mannitol lactose.
5. **Release rate retardants (5%-60%):** e.g. Dicalcium phosphate, ethyl cellulose, sodium carboxymethayl cellulose.
6. **Buoyancy increasing agents (upto80%):** e.g. Ethyl cellulose.

Method of Preparation of Floating Microspheres:

During the preparation of floating controlled release microspheres, the selection of optimal technique has utmost relevance for the efficient entrapment of energetic constituents. Selection of fabrication approach generally relies upon the character of the polymer, the drug, and their supposed use. Characteristic capabilities of substances and the procedure engineering components strongly affect properties of microspheres and the resultant controlled release rate [8, 17-18].

The practice of microspheres should satisfy certain criteria [19, 20]. They are:

(a) The capability to incorporate fairly concentrations of the drug.
(b) Stability of the guidance after synthesis with a clinically acceptable shelf-life.
(c) Controllable particle length and dispensability in aqueous vehicles for injection
(d) Release of active agent with good control over a extensive time scale.
(e) Biocompatibility &biodegradability, and
(f) Susceptibility to chemical modification.

1. Solvent Evaporation Technique [8, 21]:

This method is extensively employed by big range of pharmaceutical industries to obtain the controlled launch of drug. This approach involves the emulsification of an natural solvent (normally methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous non-stop phase, with the aid of an agitator. The awareness of the emulsifier present inside the aqueous phase impacts the particle size and shape. When the favored emulsion droplet length is formed, the stirring rate is reduced and evaporation of the natural solvent is realized below atmospheric or decreased pressure at the suitable temperature.

.2Emulsion Solvent Diffusion Method [8, 22]:

In this method solution of polymer and drug in ethanol methylene chloride is poured into an agitated aqueous solution of poly (vinyl alcohol). The ethanol hastily walls into the external aqueous section and the polymer precipitates round methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of inner cavities inside the micro particles.

.3Single Emulsion Technique [8, 19, 23]:

The microparticulate providers of herbal polymers i.e. the ones of proteins and carbohydrates are prepared by way of single emulsion technique. The natural polymers are dissolved / dispersed in aqueous medium accompanied by dispersion in the non-aqueous medium like oil with the assist of pass linking agent. In the second one step of preparation, go-linking of dispersed globule is carried out. The go linking is carried out with the aid of two methods i.e. Either via heat or via chemical go linking agents which include glutaraldehyde, formaldehyde, diacid chloride etc.

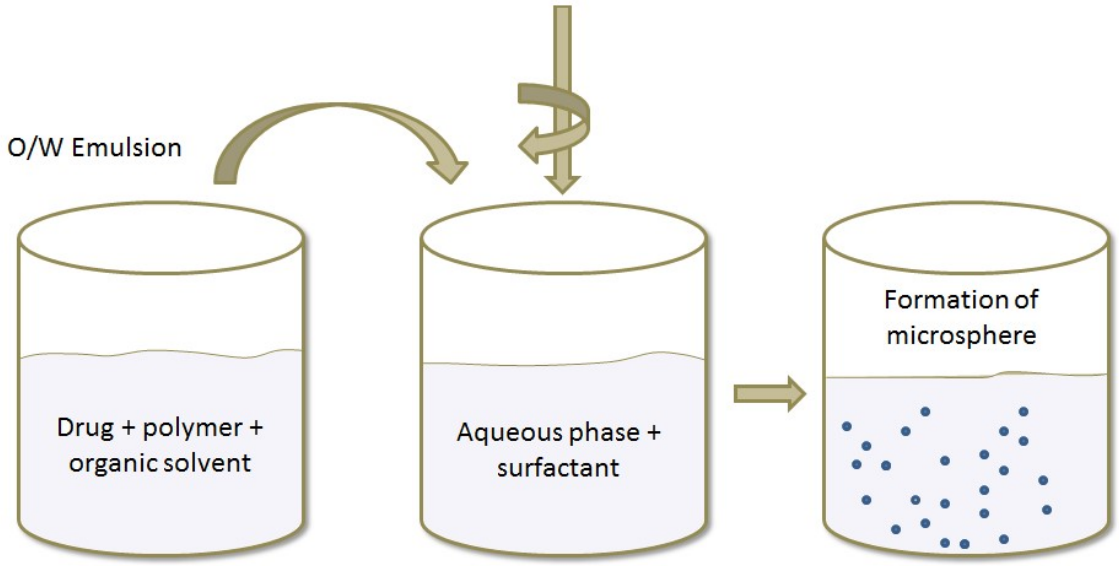

Figure 4: Solvent evaporation technique

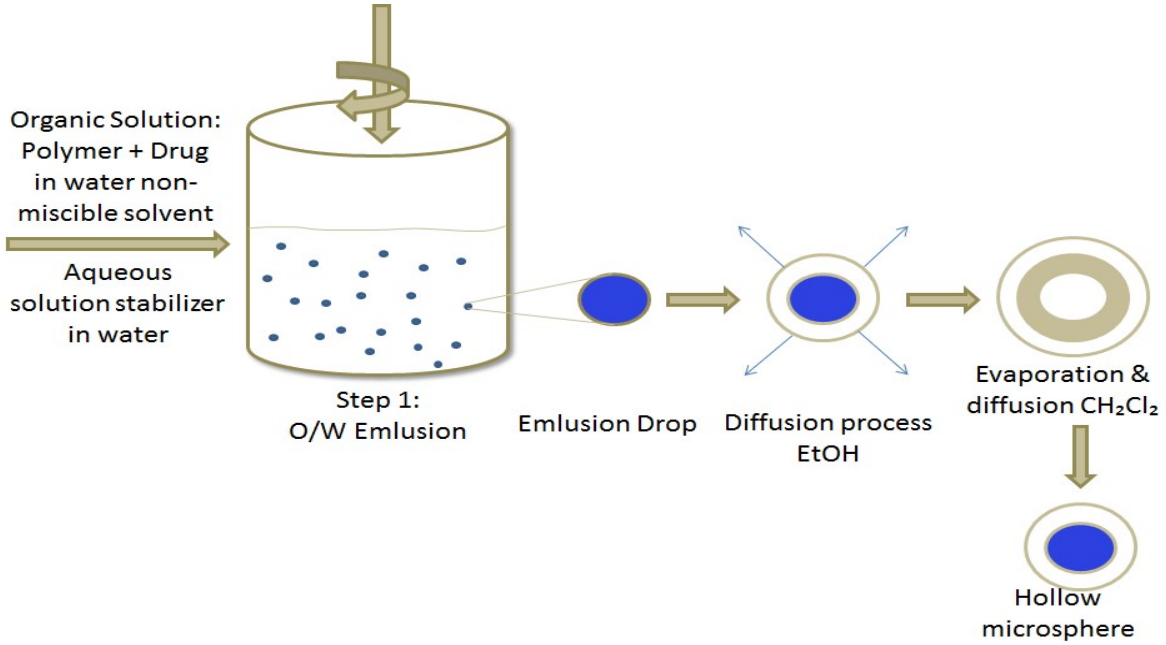

Figure 5: Emulsion solvent diffusion method

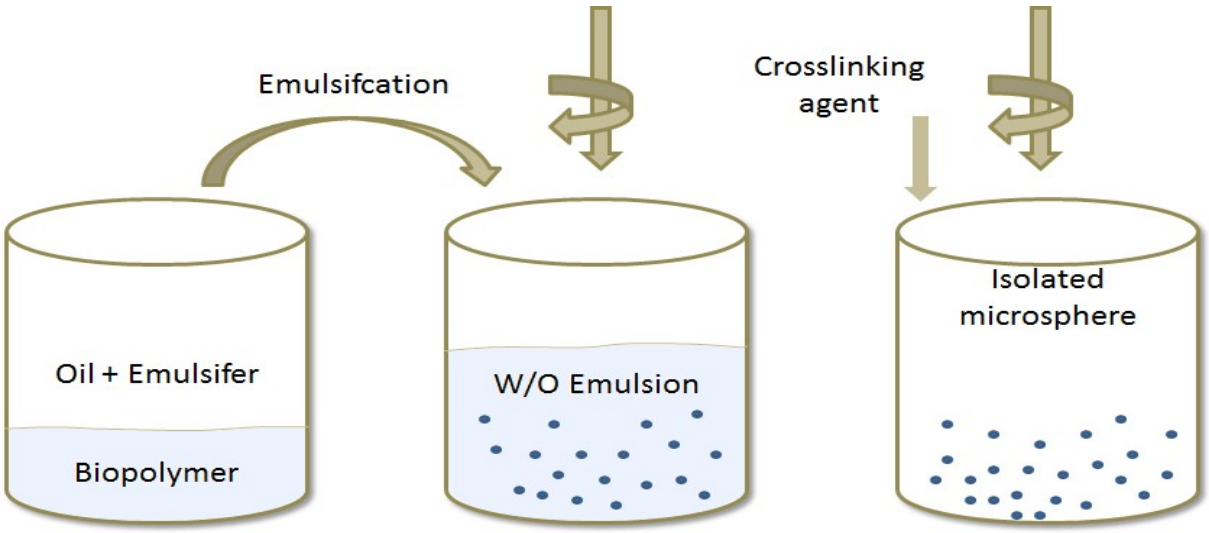

Figure 6: Single Emulsion Technique

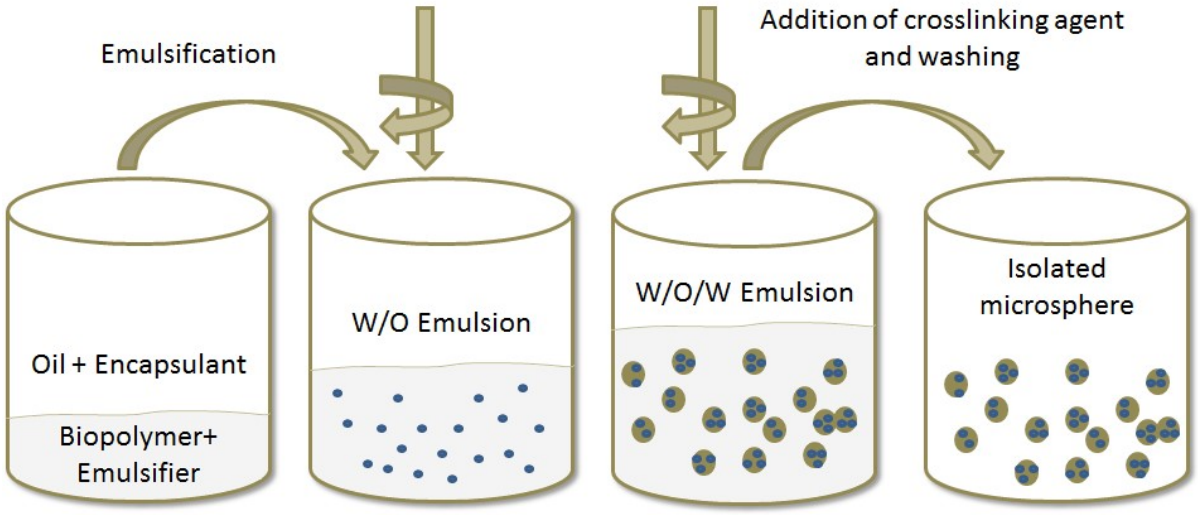

Figure 7: Double Emulsion Technique

4. Double Emulsion Technique [8, 19, 23, 24]:

This approach entails the formation of the multiple emulsion or double emulsion of type w/o/w. This technique may be used with the herbal as well as synthetic. The aqueous protein answer is dispersed in a lipophilic organic non-stop phase .This protein answer may comprise the energetic constituents. The continuous section is generally consisted of the polymer solution that ultimately encapsulates of the protein contained in dispersed aqueous segment. The primary emulsion is then subjected to the homogenisation or the sonication earlier than addition to the aqueous answer of the poly vinyl alcohol (PVA).This consequences in formation of a double emulsion. Emulsion is then subjected to solvent removal either through solvent evaporation or with the aid of solvent extraction process. The solvent evaporation is performed by maintaining emulsion at reduced pressure or by stirring the emulsion so that the natural phase evaporates out. The emulsion is then added to massive amount of water into which natural section diffuses out. The solid microspheres are sooner or later acquired by using filtration and washing with n hexane, acetone or any organic solvent to remove traces of oil from the surface.

5. Spray Drying [8, 19, 21, 23, 24]:

The polymer is first dissolved in a suitable volatile natural solvent together with dichloromethane, acetone etc. The drug inside the solid form is then dispersed inside the polymer solution under high speed homogenisation. This dispersion is then atomised in a circulation of hot air. The atomisation leads to the formation of small droplets or the excellent mist from which the solvent evaporates instantaneously leading the formation of microspheres.

6. Phase Separation Coacervation Technique [8, 19, 21]:

It is based on the principle of reducing the solubility of the polymer in organic section to affect the formation of polymer wealthy section known as co-acervates. The drug debris are dispersed in a solution of the polymer and an incompatible polymer is added to the machine which makes first polymer to section separate and engulf the drug particles.

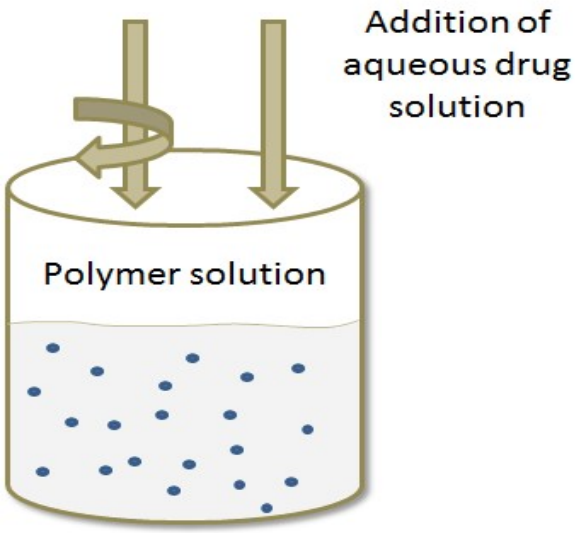

Figure 8: Phase separation coacervation technique

7. Hot Melt Encapsulation Method [8, 21]:

The performance of indomethacin microparticles and their release characteristics after coating with chitosan and gelatin, respectively, were compared by Lin WJ and Kang WW. In this instance, hot-melt encapsulation was used to create the poly (Epsilon-caprolactone) (PCL) microparticles. Because thermo-labile chemicals cannot be employed, this approach has a drawback.

Evaluation Parameters:

1. Size and Shape Evaluation:

The particle size and form plays a primary role in figuring out solubility price of the drugs and thus potentially its bioavailability. The particle size of the components was decided using Sieve analysis, Air elutriation analysis, Photo analysis, Optical microscope, Coulter counter techniques, Sedimentation techniques, Air Pollution Emissions Measurements, Laser diffraction methods, ultrasound attenuation spectroscopy, etc [15, 25-29].

2. % Yield of Microspheres:

This is calculated from weight of microspheres obtained ×100 overall weight of drug and polymer [16].

3. Entrapment Efficiency (EE%) [30-34]:

The drug is extracted by means of a appropriate method, analyzed and is calculated from:

$$EE\ (\%) = \left(\frac{W_{initial\ drug} - W_{free\ drug}}{W_{initial\ drug}}\right) x100$$

4. *In Vitro* Floating Ability (Buoyancy %) [16]:
A known amount of microspheres are unfold over the floor of a USP (Type II) dissolution apparatus packed with 900 ml of 0.1 N HCl contain 0.002% v/v Tween eighty and agitated at a hundred rpm for 12 hr. After 12 hr, the floating and settled layers are separated, dried in a dessicator and weighed. The buoyancy is calculated from the subsequent formula.

$$Buoyancy\ (\%) = \left(\frac{W_f}{W_f + W_s}\right) x100$$

Where, Wf and Ws are the weights of floating and settled microspheres respectively.

5. *In-vitro* Release Studies [15, 35-37]: *In vitro* launch studies (USP dissolution equipment LAB-INDIA Dissolution 2000) were executed to provide the quantity of the drug that is released at a particular time length. Release studies were completed by the usage of Franz diffusion cell gadget and artificial membrane as well as different types of dissolution apparatus.

Table 1: List of Drug & Polymer Used In Formulation & Method of Preparation

Sr. No.	Drug	Polymers	Method of Preparation	Reference No.
01	Esomeprazole	CA, Eudragit L100, Carbopol 940, HPMC, Acetone, Liquid Paraffin	Solvent Evaporation Technique	[38]
02	Esomeprazole Magnesium trihydrate	HPMCAS, Sodium Sulfate, Acetone, Liquid Paraffin, Span 80	Non- Aqueous Solvent Evaporation	[39]
03	Glipizide	Ethyl Cellulose, HPMC K4m, HPMC K15M, Ethanol, DCM, Tween 80	Emulsion solvent evaporation technique	[40]
04	Metformin	Eudragit RS100, HPMC	Non- Aqueous Solvent Evaporation	[41]

Table 2: Marketed Products of FDDS [2, 4, 42]

Sr. No.	Brand Name	Drug (Dose)	Company, Country	Remarks
01	Modapar®	Levodopa (100mg), Benserazide (25 mg)	Roche Products, USA	Floating CR capsule
02	CifranOD®	Ciprofloxacin (1 gm)	Ranbaxy, India	Ranbaxy, India
03	Valrelease®	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating Capsule
04	Liquid Gavison®	Al hydroxide (95 mg), Mg carbonate (358 mg)	GlaxoSmith Kline, India	Effervescent floating Liquid alginate preparation
05	Cytotec®	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
06	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid Alginate preparation
07	Conviron®	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
08	Oflin OD	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet
09	Zanocin OD	Ofloxacin	Ranbaxy, India	Effervescent floating system
10	Inon Ace Tablets	Siméthicone	Sato Pharma, Japan	Foam based floating system
11	Baclofen GRS	Baclofen	Sun Pharma, India	Coated multi-layer floating & swelling system
12	Cipro XR	Ciprofloxacin hydrochloride and betaine	Bayer, USA	Erodible matrix based system

Applications [15, 42]:

1. Sustained Release Drug Delivery System:

HBS structures can remain within the stomach for long periods and consequently can launch the drug over a prolonged period of time. The issue of short gastric home time experienced with an oral CR detailing thus can be overwhelmed with these frameworks. These frameworks have a mass thickness of <1 because of which they can skim on the gastric substance. These frameworks are generally huge in size and going from the pyloric opening is restricted.

2. Site-Specific Drug Delivery:

These frameworks are especially invaluable for API that are explicitly ingested from stomach or the proximal piece of the small digestive tract, e.g., riboflavin and furosemide.

3. Absorption Enhancement:

Drugs with low bioavailability due to site-specific absorption from the upper gastrointestinal tract are candidates for preparation as floating drug transport systems, which enhances their absorption.

CONCLUSION

Medication ingestion inside the gastrointestinal tract is a moderately factor technique and expanding the gastric maintenance of the dose shape broadens the ideal opportunity for tranquilize as similation inside the gastrointestinal tract is a particularly factor methodology and increment gastric maintenance of the dose shape broadens the ideal opportunity for sedate ingestion. In this manner gastro retentive measurement structures give an extra advantage to drugs which may be consumed basically inside the top portions of gastrointestinal tract.

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