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FLOATING MICROSPHERES: A REVIEW

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ABSTRACT

The complication with the oral drug delivery system is sustainable release and the retention of the drug in the gastrointestinal tract for release over a favourable or desirable timeline. moreover gastric emptying is one such a process that have several complex role in vivo systems which is unpredictable and not same all the time with respective drugs, so in order to avoid the variability an effort has been made to develop drug delivery system such as GRDDS(gastro retentive drug delivery system), FDDS(floating drug delivery systems)which do have greater absorptive window and high residence time in the GIT. sometimes the drug is not completely absorbed due to the emptying rate of the GIT having narrow absorption window for some drugs and moreover gastrointestinal tract physiology and transit time leads to irregular availability and lack of therapeutic effect or desired pharmacological action overall tackling all the problems. they are also advantageous than other dosage forms like the scenarios of minimization of fluctuations in drug concentrations in plasma due to sustain release, showing its effect over a prolong period, desired therapeutic effect and pharmacological action,low side effects, low dosage administration and useful for short half life of drugs and enables administration at low frequency leading to lower drug waste and also improves solubility of drugs finally they extent scope for innovative products due to there retention capacity.

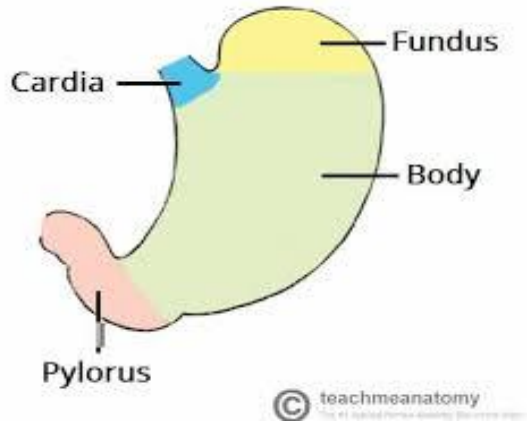
KEYWORDS: Narrow Absorption Window, Half-Life.

1.0 INTRODUCTION

Mostly changes in novel drug delivery systems have been more concerned with the safety and efficacy of the chemical compound to formulate the dosage form in the convenient method of administration. drift towards patient compliance has been observed. the oral being safe and ease of administration, cost-effectiveness, better bioavailability, and ease of handling made it one of the prioritised methods for the masses.

Coming to the conventional oral dosage forms they have been unsuccessful in lacking the good absorption property throughout the gastrointestinal tract thus lacking bioavailability and therapeutic effect. some polar drugs usually get less absorbed by the large intestine so they get absorbed only through the small intestine they use natural pathways such as receptor-mediated transport, active transport or other specific transport which are called “absorptive windows” in the small intestine. those drugs some of them might have a “narrow absorption window”, The drug released in the region prior and in close vicinity is only absorbed remaining goes into the waste. in some cases, the anatomy of the stomach may also affect the absorption and retention.

2.0 ANATOMY OF STOMACH



Not only gastrointestinal tract physiology as discussed above the orally administered controlled release dosage forms have complications of variability in the retention time and gastric emptying rate under normal gravity conditions.

To have a great absorption the drug need to have a great retention property and should float to stay for a particular retention time so here are the factors that affect gastric retention.

3.0. FACTORS AFFECTING GASTRIC RETENTION

3.1. The particle size should be around 1 to 2 mm in order to pass through the pyloric valve into the small intestine.

3.2. basic drugs are better absorbed in the fed state due to PH (4 to 6) which is far better than no gastric acid, as stomach takes time to secrete gastric juice immediately after liquid emptying hence is the main reason even at high PH of stomach at fasting state(1 to 2)basic drugs does not dissolve or absorbed.

3.3. it is proven fact such as nutritive property in the stomach affects the drug emptying property which is administered along with the food like caloric value as the calories in the food increases it takes more time to leave the tract which is the gastric emptying time.

3.4. biological factors such as age, gender, sex, posture, disease state, BMI index also affects the gastric emptying such as females do have less gastric emptying property than that of males

4.0 SYSTEMS NEED TO FORM FLOATING MICROSPHERES ARE

4.1) High-density systems
4.2) Expandable systems
4.3) Floating systems
4.4) Magnetic systems
4.5) Mucoadhesive or bioadhesive systems
4.6) Super porous hydrogels

5.0 MECHANISM OF FLOATATION OF MICROSPHERES ARE

A need to achieve buoyancy. it can be achieved by minimal gastric content such as gastric fluid which enters into the device consists of gel formers, polysaccharide layers, polymers which hydrates to form colloidal gel barrier which controls fluid penetration pattern. the exterior surface gets dissolved and the gel layer is maintained by getting hydration from the hydrocolloid layer, the air trapped by the polymers lowers the density and hence maintains buoyancy.

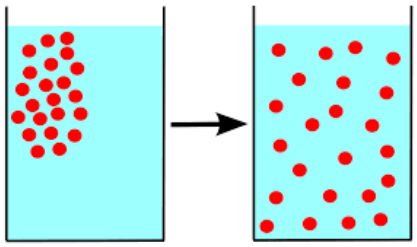
6.0 MECHANISM OF GASTRIC RETENTION

Adherence is assumed to be achieved during both fed states and fasting states only considering the mucoadhesive property of the particle is not altered by the stomach contents in particular non-adherent mucus.

7.0 MECHANISM OF DRUG RELEASE FROM THE MICROSPHERE ARE

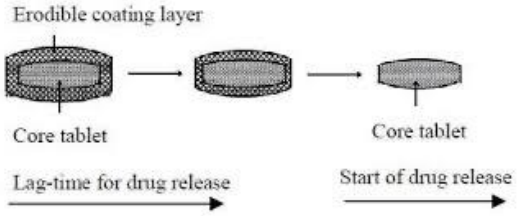
7.1 Diffusion

On contact with the gastric fluid, drug dissolution takes place and the drug solution diffuses across through the exterior coat.



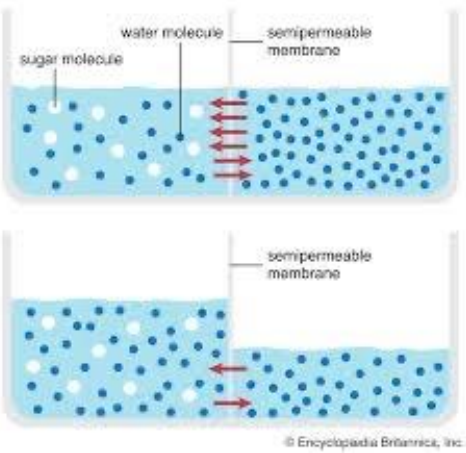
7.2. Erosion

Coatings usually get eroded with time and release the medicament or the drug.



7.3 Osmosis

The water is entered into the dose under specific circumstances and there builts an osmotic pressure wherein leads to the release of the drug into the exterior.

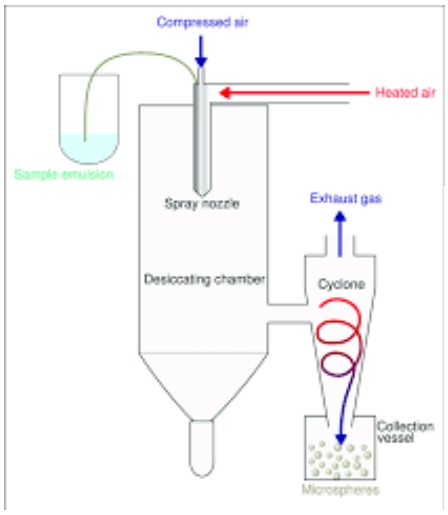


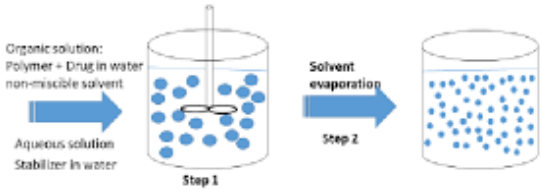
8.0 METHODS OF PREPARATION

8.1. Spraydrying

The liquid feed material is atomized into small droplets. This can be achieved using various atomization methods, including pressure nozzles, rotary atomizers, or pneumatic atomizers. The aim is to create a large surface area for efficient drying. The atomized droplets are introduced into a drying chamber where they come into contact with a stream of hot air or gas. The hot gas acts as the drying medium and facilitates the evaporation of the liquid from the droplets. The droplets and hot gas move concurrently or counter currently through the chamber, depending on the specific process configuration. As the droplets come in contact with the hot gas, the liquid rapidly evaporates, leaving behind solid particles. The heat transfer from the hot gas to the droplets causes the remaining moisture to evaporate,

resulting in the formation of dry particles. The drying process occurs very quickly due to the large surface area-to-volume ratio of the droplets. Particle collection: Once the particles are formed, they are separated from the drying air. This is typically done using cyclone separators or bag filters, where the particles are collected while the drying air is recycled or vented. The collected particles may require further processing, such as milling or sieving, to achieve the desired particle size distribution.



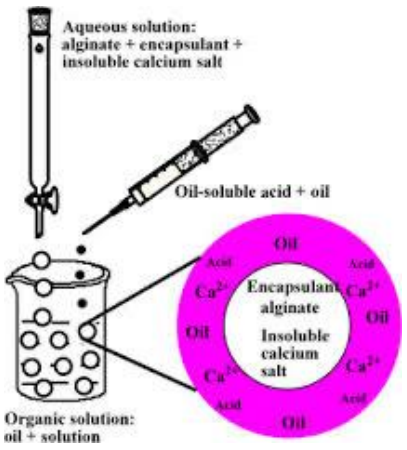


8.2 Solvent evaporation method

A solution or suspension is prepared by dissolving the desired solid material (e.g., polymers, drugs, or nanoparticles) in a suitable solvent. The solvent should have a relatively high vapour pressure to facilitate efficient evaporation. The solution or suspension is deposited or cast onto a substrate or into a mould depending on the desired final product. The substrate or mould can be made of various materials, including glass, silicon, or polymers, depending on the application. The deposited solution or suspension is then subjected to conditions that promote solvent evaporation. This can be achieved by exposing it to ambient air, heating, or applying a vacuum depending on the volatility of the solvent. As the solvent evaporates, the solid material forms a thin film, coating, or precipitates as particles. As the solvent evaporates, the solid material gradually solidifies, resulting in the formation of a solid film, coating, or particles. The drying process can be accelerated by applying heat or using airflow to enhance solvent removal. Once the solvent has completely evaporated, the solid material may undergo further post-processing steps, such as annealing, curing, or surface modification, to improve its properties or functionality. This step is highly dependent on the specific material being processed.

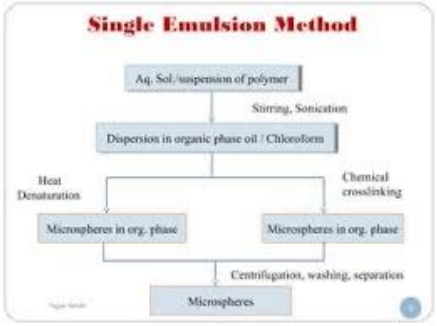
8.3 Ionic gelation method

In this process, cross-linking agent, polymer and copolymers were dissolved in the pure water to form homogenous mixture now the core is made to be mixed in the polymer solution using a magnetic stirrer to form a homogenous dispersion. the gelation medium is formed by adding calcium chloride in 2% glacial acetic acid. The homogenous alginate solution is extruded into the gelation medium using a syringe finally formed microspheres were collected and washed with distilled water twice and dried at room temperature for about 24 hr.



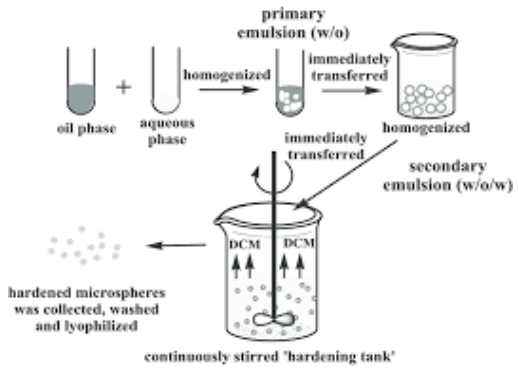
8.4 Single emulsion technique

In this process, the natural polymers are dissolved in the aqueous medium which is dispersed in the non-aqueous medium like oil. In the next step, the cross-linking of the globule is carried out. it can be achieved by heat or by using chemical crosslinkers.



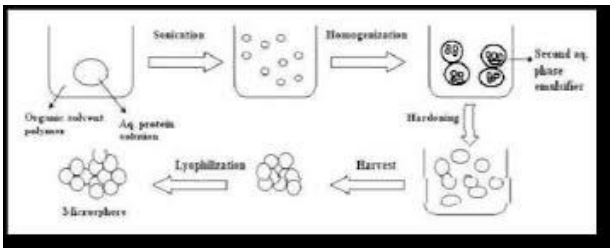
8.5 DOUBLE EMULSION METHOD

In this process, the formation of the multiple emulsion is seen like that of W/O/W .in this process continuous phase consists of a polymer solution that gets encapsulated of protein contained in the dispersed aqueous phase then the primary emulsion is subjected to the homogenization results in the formation of a double emulsion. This method is best suited for water-soluble drugs, proteins, peptides, and vaccines.



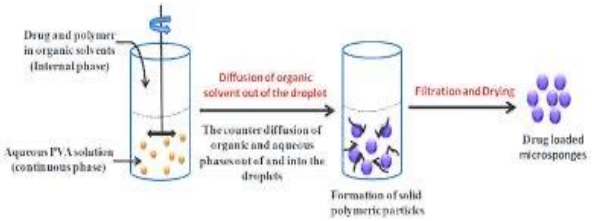
Phase separation coacervation technique:

In this method, the drug particles are made to be dispersed in the polymer solution and then an incompatible polymer is added to the system which makes the separation of the first polymer to avoid agglomerates the suspension is made to stir at a suitable speed which leads to the formation of the microspheres.



8.6 Quasi-emulsion solvent diffusion

A hydrophobic polymer, such as poly(lactic-co-glycolic acid) (PLGA), is dissolved in an organic solvent, typically dichloromethane (DCM) or chloroform. The polymer concentration and the choice of solvent depend on the desired particle size and the properties of the drug or substance to be encapsulated. The polymer solution is then mixed with an aqueous phase containing a surfactant. The surfactant helps in stabilizing the emulsion and preventing the coalescence of polymer droplets. Typically, a high-shear mixing technique, such as sonication or homogenization, is employed to obtain a stable oil-in-water emulsion. The emulsion is then subjected to controlled agitation or mild heating, which facilitates the diffusion of the organic solvent (DCM or chloroform) from the dispersed polymer droplets into the continuous aqueous phase. As a result, the polymer droplets solidify and form nanoparticles or microspheres, entrapping the hydrophobic drug or substance within the polymer matrix. The polymer particles continue to harden as the solvent diffusion progresses. Once the solvent has completely evaporated or diffused, the solidified particles can be collected by centrifugation, filtration, or freeze-drying. The collected nanoparticles or microspheres can then be further processed or used for drug delivery applications.



9.0 CHARACTERISTICS OF FLOATING MICROSPHERES

The evaluation of microspheres is conducted by possession of micrometric properties such as bulk density, true density etc.

9.1) MICROMERITICS

It deals with the fundamental and derived properties of individual particles.

A. PARTICLE SIZE

The size of individual particles is found by the compilation of particle sizes of approximately 200 to 300 by the method of an optical microscope with the usage of the ocular micrometer Particle size analysis and distribution is found by the sieve shaking method.

Average particle size can be found out by using the following formula:-

Mean particle size = Σ (mean particle size of the fraction × weight fraction)/Σ (weight fraction)

B. BULK DENSITY

It is calculated using a weight of the powder and the volume occupied by the powder without any disturbance

Bulk density =Weight of sample/Volume of sample

C. TAPPED DENSITY

It is calculated using mass of the powder and the volume occupied by the powder after tapping the powder

Tapped density=mass of powder/tapped volume of the powder

D. CARR'S INDEX

It tells about the flowability property of powder

It is calculated using the following formula

Carr′s index (%) = [(Tapped density − Bulk density)/ Tapped density] × 100

A Carr's index greater than 25% is found to have poor flowability and Carr's index less than 15% is found to have good flowability.

E. ANGLE OF REPOSE

The angle of repose defines the flowability of the powder is found out by using the practical way by allowing the flowability through the funnel and measuring the height and diameter, radius of the pile obtained

$$\theta = \tan^{-1} h/r$$

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

F. HAUSNER'S RATIO

Hausner's ratio defines the flowability of the powder.it is an indication of the compressibility of the powder.it is found out by the following formula

Hausner′s ratio = (Tapped density/Bulk density)× 100

The Hausner's ratio is greater than 1.25 and is found to have poor flowability

9.2) PERCENTAGE YIELD

It is the true product produced than the product needs to be obtained and is generally found out by the actual yield divided by the theoretical yield multiplied by 100.it is found out that actual yield is always less than theoretical yield due to various reasons such as the product lost during the procedure and process.

% yield = (actual weight of floating microspheres/weight of drug taken + total polymer weight) ×100

9.3) DRUG ENTRAPMENT EFFICIENCY

Just as that of percentage yield this is the special property of microspheres evaluation it can be found by the following procedure:-

1) Microspheres are crushed at first
2) Those microspheres were mixed by using 0.1N HCL aliquots repeatedly
3) Then it is made up to the volume of 100 ml measuring cylinder
4) Finally absorbance of the following extract using a spectrophotometer and comparing it against blank

DEE = (amount of drug actually present/theoretical drug load expected) × 100

9.4) SURFACE MORPHOLOGICAL STUDIES

The internal and external morphology of the microspheres can be studied by using the scanning electron microscopy

9.5) IN VITRO BUOYANCY/FLOATING BEHAVIOUR

In this method, the microspheres were spread across the dispersed medium containing(900 ml of 0.1N HCL and 80 tweens surfactant) which is known as dissolution medium. this dissolution medium is agitated with a paddle at a rotation per minute of 100. after settling for 12 hours without any disturbance both the floating and settled microspheres were collected separately. microspheres were collected, dried and weighed and the percentage buoyancy is calculated using the following formula by the obtained weights.

Percentage Buoyancy = Wf / Wf + Ws.

Where,

Wf = mass of floating microspheres

Ws = mass of settled microspheres

9.6) DISSOLUTION TEST(IN VITRO DRUG RELEASE) OF MICROSPHERES

In this method, the known amount of drug microspheres are filled in the hard gelatin capsules and placed in a dissolution medium of 900ml in a basket and agitated with a paddle at rotation per minute 100 at 37 ± 0.5°c. the samples are drawn at the specified time interval to study the dissolution studies using UV spectroscopy as the analytical method of the amount of drug release.

9.7) IN VIVO STUDIES

This process is usually conducted in living beings such as male albino rats, human beings, and beagle dogs where the stomachs are usually filled with the drug and dissolution studies were studied using barium sulphate by performing the X-ray photography technique. urinary excretion data of the species were collected to study pharmacokinetic studies.

9.8) STABILITY STUDIES

This method is used to test the shelf life of microspheres by using the stability chambers which enable to maintain of temperatures and humidity. Finally the physical appearance and the drug content are studied.

10.0 APPLICATIONS OF FLOATING MICROSPHERES

Floating microspheres are specifically used to improve the absorption property of the drugs which have a narrow absorption window thereby enhancing bioavailability by having the following mechanisms:-

10.1 SUSTAINED DRUG RELEASE SYSTEM

These microspheres are hydrodynamically balanced systems which are having a bulk density less than 1 wherein they can stay in the short stomach for a long period time as they can float through out the stomach.

10.2 SITE SPECIFIC DRUG DELIVERY SYSTEM

These systems are specially and more specifically easily absorbed in the stomach and small intestine at the proximal part.

10.3 ABSORPTION ENHANCEMENT

The drugs which are having less absorption window and poor bioavailability are benefitted from having floating drug delivery systems as they can increase bioavailability.

10.4 MAINTAINANCE OF CONSTANT BLOOD LEVEL

These systems ensure easy patient compliance and have constant blood levels.

10.5 AS CARRIERS

Floating microspheres are formulated mainly as a carrier medium for drugs like antifungal, antiviral and antibiotic agents which have a specific characteristic so-called as absorption window.

10.6 OVER COMING SIDE EFFECTS

Non-steroidal anti-inflammatory drugs which usually come with adverse affects such as gastric irritation is abolished if the medicament is formulated as floating microspheres.

10.7 ENHANCEMENT OF THE INSOLUBLE/SPARINGLY SOLUBLE DRUGS

Floating microspheres increase the solubility of poorly and sparingly soluble substances hence increasing the solubility of the drugs.

10.8 RELIEF FROM ULCERS

Floating microspheres are microbeads which exhibit their effect by local release and increase their concentration at the mucosal site and eradicate helicobacter pylori and hence gives relief from gastritis and duodenal ulcer, oesophagitis.

Dosage form	Drug (s)
Microspheres	Aspirin, griseofulvin and p-nitroaniline Ibuprofen, Terfenadine, Tranilast
Granules	Diclofenac sodium, Indomethacin, Prednisolone
Films	Cinnarizine, Drug delivery device
Powders	Several basic drugs (63)
Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-Dopa and benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid
Tablets/Pills	Acetaminophen, acetylsalicylic acid, amoxycilin trihydrate, ampicilin, atenolol, Chlorpheniramine maleate, Cinnarizine, Diltiazem, Fluorouracil, Isosorbide dinitrate, p- Aminobenzoic acid, Piretanide, Prednisolone, Quinidine gluconate, Riboflavin-5'-phosphate, Sotalol, Theophylline, Verapamil

Table 1: List of drugs explored for developing floating dosage form

11.0 MARKETED PRODUCTS OF FDDS

Drug	Commercial name	Company
Risperidone	RISPERDAL® CONSTA®	Janseen®/Alkermes, Inc
Naltrexone	Vivitrol®	Alkermes
Leuprolide	Lupron Depot®	TAP
	Enantone Depot®	Takeda
	Trenantone®	Takeda
	Enantone Gyn	Takeda
Octreotide	Sandostatin®LAR	Novartis
Somatropin	Nutropin®Depot	Genentech/Alkermes
Triptorelin	Trelstar™ Depot	Pfizer
	Decapeptyl® SR	Ferring
Buserelin	Suprecur® MP	Sanofi-Aventis
Lanreotide	Somatuline® LA	Ipsen-Beafour
Bromocriptine	Parlodel LAR ™	Novartis
Minocycline	Arestin®	Orapharma

12.0 ADVANTAGES

It is highly advantageous in the treatment of stomach disorders.

Drugs with a short half-life as well as drugs which are metabolized in the upper GIT or drugs that have specific absorption centres in the stomach or the proximal part of the small intestine can be made into this system to get a maximal therapeutic effect.

These drugs can be used to overcome the adversities of gastric retention time as well as the gastric emptying time.

The active ingredient is made to release over an extended period.

The active entity is delivered to the specific site thus eliminating side effects.

Concentration fluctuations can be reduced.

The drug can be absorbed throughout the stomach.

Sometimes acidic drugs such as aspirin may irritate the stomach wall hence FDDS can be useful for the administration of certain drugs.

Finally Provides greater therapeutic and bioavailability properties.

13.0 DISADVANTAGES

The major disadvantages of floating microspheres are:-
Sometimes buoyancy can never be predicted b; coz of the factors such as gastric motility, ph, and presence of food.

Drugs that cause gastric irritation and lesion are not suited to formulate as FDDS.

High variability in the gastric emptying process.

Patients should not be dosed with FDDS just going before to the bed.

FDDS cannot be formulated for drugs of low solubility.

GRDS need to be administered with fluids.

The drugs which metabolize through first-pass metabolism are not formulated in this form.

These systems also require the presence of food to delay their gastric empty.

14.0 CONCLUSION

GRDS and FDDS commonly known as floating microspheres known to increase the bioavailability of those drugs who have extensive first-pass metabolism or

low bioavailability or absorptive window so these techniques are commercialized for their benefits.

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