

FLOATING MICROSPHERE: A NOVEL GASTRORETENTIVE DOSAGE FORM

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ABSTRACT

Almost drugs are rapidly and completely absorbed from gastrointestinal tract. But some drug having problems like first pass metabolism, low bioavailability, chances of dose dumping, unstability at colonic pH, produced gastric irritation when administered in single unit dosage form or disturbed normal colonic bacterial flora. It creates the need to design safer and effective drug delivery systems. The floating microspheres are one of the most promising multiparticulates drug delivery system which offers numerous applications including targeting site with specificity, maintain concentration at site of interest without untoward effects, controlled release of drug, improve efficacy, reduced toxicity, improve patient compliance and physicochemically stable. They are spherical and characteristically free flowing powder having particle size range is between 1 to 1000 μm . Floating microspheres are administered by filling in hard gelatin capsule. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials. The purpose of this review is to highlights various types of microspheres, different methods of preparation, applications and evaluation parameters of floating microspheres.

Keywords: low bioavailability, dose dumping, gastric irritation, floating microspheres.

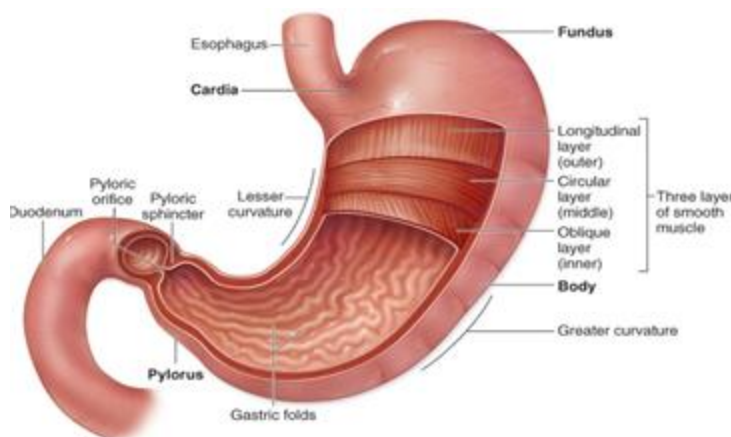
INTRODUCTION

The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Due to its advantages like more convenient, safe, least expensive and self-medication is possible.

ANATOMY AND PHYSIOLOGY OF STOMACH: ⁰⁶

The stomach is a "J" shaped enlargement of the GI tract directly inferior to diaphragm in the epigastric, umbilical and left hypochondriac regions of the abdomen. The stomach has four main regions – Cardia, Fundus, Body and Pylorus.

Fig-1: Anatomy and Physiology of Stomach



1. **Cardiac:** Surrounds the superior opening of the stomach.
2. **Fundus:** The rounded portion superior to and to the left of the cardia.
3. **Body:** Inferior to the fundus is the large central portion of the stomach.
4. **Pylorus:** The region of the stomach that connects to duodenum. It has two parts: 1.pyloric antrum, 2.pyloric canal Stomach lining consist of considerable number of gastric pits that contribute to the storage capacity of stomach. Antrum region responsible for mixing and grinding of gastric content. Under fasting state stomach is a collapsed bag with residual volume of 50 ml and contains small amount of gastric fluid (pH 1-3) and air. Mucus secreted by goblet cells and gastric acid by oxyntic (parietal) cells.

MOBILITY PATTERN OF STOMACH:

There are two distinct modes of GI motility and secretory pattern in humans and animals in fasted and fed state. Fasted state is associated with various cyclic events regulating the GI motility patterns, commonly called as the migrating motor complex (MMC). MMC is organized into alternating cycles of activity and subdivided into basal, preburst, burst intervals also name as phase1, 2 and 3.

Phase 1:

The quiescent period last from 30-60min and is characterized by lack of any secretory and electrical activity and contractile motion.

Phase 2:

Exhibits intermittent action potential for 20-40 min with increasing contractile motions. Bile enters the duodenum during this phase while the gastric mucus discharge occurs during later part of phase 2 and throughout phase 3.

Phase 3:

Shows the prevalence of intense large and regular contraction that sweep off the undigested food. These are also called 'housekeeper waves' and propagate for 10-20min.

Phase 4:

This is the transition period of 0-5 min between phase 3 and phase 1. These inter digestive series of electrical events originates in foregut and propagate to terminal ileum in the fasted state and repeat cyclically every 2-3h.

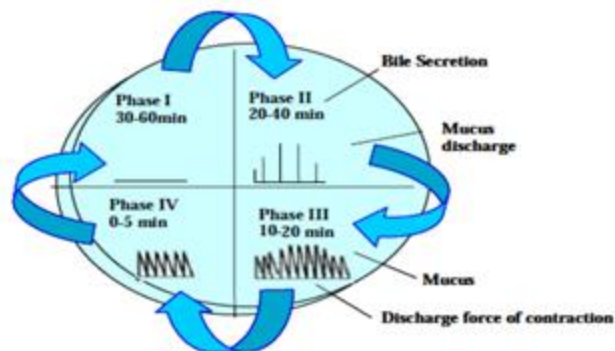


Fig-2: Gastric mobility pattern

GASTRO RETENTIVE DRUG SYSTEM:⁰⁸

DELIVERY

Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby, improve the bioavailability of drugs. If the drugs are poorly soluble in the intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in gastrointestinal absorption of drugs with narrow therapeutic absorption window, as well as, controlling release of drugs having site specific-absorption limitation. Drugs that could take advantage of gastric retention include the drugs whose solubility is less in the higher pH of the small intestine than the stomach (e.g. Chlordiazepoxide and Cinnarizine), the drugs prone for degradation in the intestinal pH (e.g. Captopril) and the drugs for local action the stomach (e.g. Misoprostol). Antibiotics, Catecholamines, Sedatives, Analgesics, Anticulvulsants, Muscle relaxants, Antihypertensives and Vitamins can also be administered in HBS dosage form.

Conventional drug delivery system Vs Gastroretentive drug delivery system:⁰⁸

Conventional drug delivery system	Gastroretentive drug delivery system
○ High risk of toxicity	● Very low risk of toxicity
○ Less patient compliance	● Improve patient compliance
○ Not suitable for drugs having narrow absorption window in intestinal region	● Suitable for drugs having narrow absorption window in intestinal region
○ Not suitable for drugs that degrade in colonic pH	● Suitable for drugs that degrade in colonic pH
○ Not suitable for drug that act locally in stomach	● Suitable for drugs that act locally in stomach
○ Not suitable for drugs that disturb normal colonic bacteria	● Suitable for drugs that disturb normal colonic bacteria.
○ Risk of dose dumping	● No risk of dose dumping

Table-1 Conventional drug delivery system Vs Gastroretentive drug delivery system

Current approaches to GRDDS:^{07,08,09,15,}

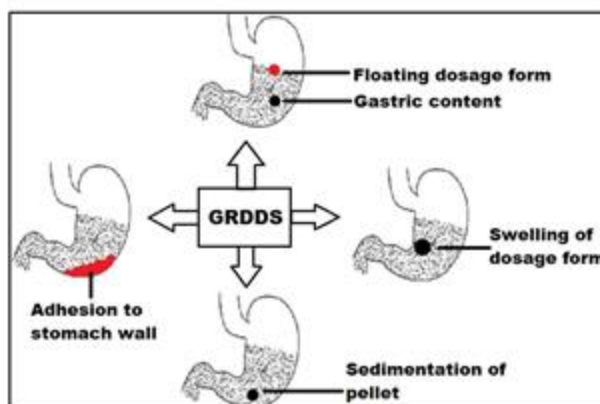


Fig-3: Types of GRDDS

1. Floating drug delivery systems (FDDS):

Floating systems was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. Floating systems can be classified as follows.

a. Single unit dosage form:

i. Effervescent system:

Effervescent floating drug delivery systems generate gas (CO₂), thus reduce the density of the system, and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at a desired rate. The main ingredients of effervescent system include swellable polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate and tartaric acid.

ii. Noneffervescent system:

Noneffervescent systems commonly use gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel forming hydrocolloid. After oral administration, this dosage form swells in contact with gastric fluids and attains a bulk density of less than 1 g/ml. The air entrapped within the swollen matrix imparts buoyancy to the dosage form.

b. Multiple unit dosage form:

Multiple unit dosage forms may be an attractive alternate since they have been shown to reduce inter and intra-subject variabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple unit floating systems have been developed in different forms, and using principles such as air compartment multiple unit system, hollow microspheres prepared by emulsion solvent diffusion method, beads prepared by emulsion gelation method. Use of effervescent and swellable polymer is another approach for preparing multiple unit FDDS.

i. Effervescent system:

The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO₂ was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0g/ml. It was found that the system had good floating ability independent of pH and viscosity and the drug (Paraamino benzoic acid) released in a sustained manner.

ii. Noneffervescent system:

Not many reports were found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion processes reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

1. **Hollow microspheres:**

Both natural and synthetic polymers have been used to prepare floating hollow microspheres. The microspheres were prepared by the solvent evaporation technique.

2. **Raft forming system:**

Raft forming systems have received much attention for the drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft float on gastric fluids because of low bulk density created by the formation of CO₂. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids.

2. **Mucoadhesive systems:**

Mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and increase the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability. A mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bio-adhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). The characteristics of these polymers are molecular flexibility, hydrophilic functional groups, and specific molecular weight, chain length, and conformation. Furthermore, they must be nontoxic and non-absorbable, form noncovalent bonds with the mucin-epithelial surfaces, have quick adherence to moist surfaces, easily incorporate the drug and offer no hindrance to drug release, have a specific site of attachment and be economical. The binding of polymers to the mucin-epithelial surface can be subdivided into three broad categories.

a. **Hydration-mediated adhesion:**

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

b. **Bonding-mediated adhesion:**

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., Vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

c. **Receptor-mediated adhesion:**

Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

3. **Swelling/ Expanding Systems:**

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as *plug type systems* because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. These systems

also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration.

4. High-density systems:

Gastric contents have a density close to water ($\sim 1.004 \text{ g/cm}^3$). When high density pellets is given to the patient, it will sink to the bottom of the stomach and are entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. Sedimentation has been employed as a retention mechanism for high density systems. A density $\sim 3 \text{ g/cm}^3$ seems necessary for significant prolongation of gastric residence time. Barium sulphate, zinc oxide, iron powder, titanium dioxide may be used to formulate such high density systems due to their high density. The only major drawbacks with this systems is that it is technically difficult to manufacture them with a large amount of drug ($>50\%$) and to achieve the required density of $2.4\text{--}2.8 \text{ g/cm}^3$.

5. Magnetic systems:⁰⁷

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach.

6. Raft systems:⁰⁷

Raft systems incorporate alginate gels these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating.

Factors affecting on Gastric Retention:⁰⁷

1. Density:

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Therefore density of the dosage form should be less than the gastric contents (1.004 gm/ml). A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

2. Size and Shape:

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm . The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GIT retention 90 to 100 % retention at 24 hours compared with other shapes. When liquid and digestible solids are present in the stomach, it contracts ~ 3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed.

3. Fed or Unfed State:

The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the Migrating Myoelectric Complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

4. Nature of the meal:

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

5. Caloric Content:

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

6. Frequency of feed:

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC²⁰. Food intake and its nature Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

7. Gender:

Mean ambulatory GRT in meals (3.4 ± 0.4 hours) is less compared with their age and race-matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

8. Age:

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

9. Posture:

GRT can vary between supine and upright ambulatory states of the patients. A comparison was made to study the affect of fed and non-fed stages on gastric emptying. For this study all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at normal time intervals. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention.

Advantages of multiparticulate drug delivery over single unit dosage form:⁰⁵

- ✓ It spread out more uniformly in the GIT, thus avoiding exposure of the mucosa locally to high concentration of drug.
- ✓ Ensure more reproducible drug absorption.
- ✓ The risk of dose dumping also seems to be considerably lower than with single unit dosage form.
- ✓ Allow the administration of much smaller doses than are normally required.
- ✓ This reduces local irritation when compared to single unit dosage forms.
- ✓ Drug discharge in the stomach may be hindered and local unwanted effects may be reduced or eliminated.
- ✓ Posses many other advantages such as high bioavailability, rapid kinetic of absorption and improvement of patient compliance.
- ✓ Received much attention not only for prolonged release, but also for the targeting of anticancer drugs to the tumour.

MICROSPHERES:

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 1000 μm . Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects. This microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities or masking of unpleasant taste. Hence, they play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects. The range of techniques for the preparation of microspheres offers a variety of opportunities to control drug administration issue. This approach allows the accurate delivery of small quantity of the potent drugs, reduced drug concentration at the site other than the target site and the protection of the labile compound before and after the administration and prior to the site of action.⁰¹

Routes of administration:⁰¹

Microspheres can be used for the delivery of drugs via different routes. Route of administration is selected depending on the drug properties, disease state being treated and the age and condition of the patient. Desirable properties of the microspheres to be used for the delivery will also change depending on the route of administration.

1. Oral delivery:

Oral delivery is the simplest way of drug administration. In oral drug delivery, the microspheres have to pass through frequently changing environment in the GI tract. There is also patient to patient variation in GI content, stomach emptying time and peristaltic activity. Although constants of the oral route are numerous, on the whole, it offers less potential danger than the parenteral route. The relatively brief transit time of about 12 hr through the GI tract limits the duration of action that can be expected via the oral route. Bioavailability of drugs with limited solubility in the stomach or intestine and small absorption rate constant can be increased by increasing the retention time in the stomach.

2. Parenteral delivery:

Most of the microsphere base controlled delivery systems are developed with the purpose of using them for parenteral administration. Microspheres used for parenteral delivery should be sterile, free from impurities and should be dispersible in a suitable vehicle. Hydrophilic microspheres have the potential advantage of aqueous dispersibility as opposed to hydrophobic microspheres for reconstituting them for injection. Surfactants in small concentrations are necessary for reconstituting hydrophobic particles for injection in aqueous vehicle which are reported to cause adverse tissue reaction and affect the release of the incorporated drug.

Types of microspheres:⁰¹**1. Bioadhesive microspheres:**

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

2. Magnetic microspheres:

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses towards a magnetic field from incorporated materials magnetic microspheres. They are used to deliver chemotherapeutic agent to liver tumor. The different types are therapeutic magnetic microspheres and diagnostic microspheres.

a. Therapeutic microspheres:

It is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.

b. Diagnostic microspheres:

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

3. Floating microspheres:

In floating types the bulk density of microspheres is less than the gastric fluid, so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.

4. Radioactive microspheres:

Radio immobilization therapy microspheres sized 10-30 nm is of larger than capillaries and gets trapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are emitters, β emitters, α - emitters. Biodegradable polymeric microspheres natural polymers prolongs the residence time with in body parts when contact with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of different types of hydrophilic and hydrophobic polymers.

5. Polymeric microspheres:

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

a. Biodegradable polymeric microspheres:

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.

b. Synthetic polymeric microspheres:

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

Advantages of microspheres:^{02,03,04}

1. Microspheres spread out more uniformly in the GIT, thus avoiding exposure of the mucosa locally to high concentration of drug.
2. Microspheres ensure more reproducible drug absorption.
3. The risk of dose dumping also seems to be considerably lower than with single unit dosage form.
4. Microspheres allow the administration of much smaller doses than are normally required.
5. This reduces local irritation when compared to single unit dosage forms.
6. Drug discharge in the stomach may be hindered and local unwanted effects may be reduced or eliminated.
7. Microspheres possess many other advantages such as high bioavailability, rapid kinetic of absorption and improvement of patient compliance.
8. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour.
9. Taste and odor masking.
Eg: Fish oils, sulfa drugs
10. Protection of drugs from environment
11. Particle size reduction for enhancing solubility of the poorly soluble drug.
12. Sustained or controlled drug delivery Eg: KCl, Ibuprofen.
13. Targeted release of encapsulated material.
14. Live cell encapsulation. Eg: Resealed erythrocytes.
15. Conversion of liquid to free flowing solids.
16. Delay of volatilization.
17. Separation of incompatible components Eg: Excipients, buffers and other drugs.
18. Improvement of flow of powder.
19. Safe handling of toxic substances.
20. Aid in dispersion of water insoluble substance in aqueous media

Disadvantages microspheres: ^{02,03,04}

1. The costs of the materials and processing of the controlled release preparation, which may be substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation or agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

Material used in preparation of microspheres: ³⁴

Microspheres used usually are polymers. They are classified as follows

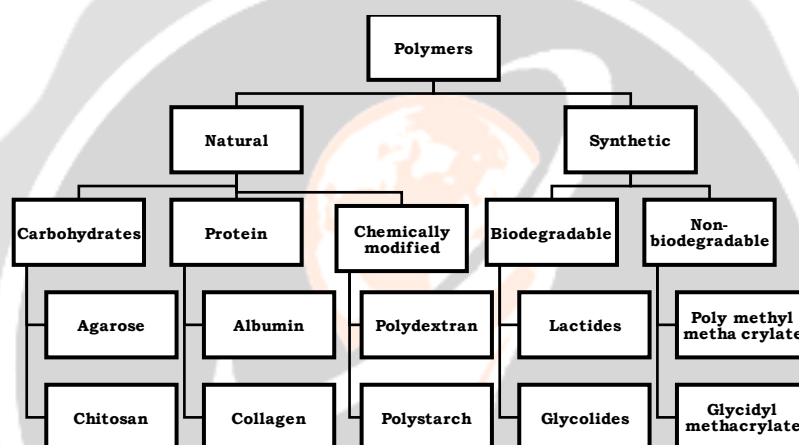


Table-2: Material used in microspheres preparation

Methods of preparation of microspheres: ^{02,07,08,15,09}**1. Emulsion solvent evaporation technique:**

Drug is dissolved in polymer which was previously dissolved in volatile organic solvent and the resulting solution is added to aqueous phase containing emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs.

2. Emulsion cross linking method:

In this method drug was dissolved in aqueous gelatin solution which was previously heated for 1 hr at 40°C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35°C, results in w/o emulsion then further stirring is done for 10 min at 150°C. Thus the produced microspheres were washed respectively three times with isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hours for cross linking and then was treated with 100mL of 10mm glycine solution containing 0.1 %w/v of tween 80 at 37°C for 10 min to block unreacted glutaraldehyde. Examples of this technique are Gelatin microspheres.

3. Double emulsion technique:

This method can be used with both the natural as well as synthetic polymers. 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 encapsulates 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 poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. Then collect microspheres by filtration and washed with demineralized water.

4. **Co-acervation method:**

In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer.

5. **Spray drying technique:**

The two processes are named spray drying and spray congealing. The polymer is first dissolved in a suitable volatile organic solvent. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1 -100 μm .

6. **Hydroxyl appetite (HAP) microspheres in sphere morphology:**

This was used to prepare microspheres with peculiar spheres At first o/w emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co-solvening and helped them to stay individual droplets. While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.

7. **Chemical Methods:**

This method uses monomers/prepolymers as starting materials. These methods involve chemical reactions along with microsphere formation. These include suspension polymerization, emulsion polymerization, dispersion and interfacial methods. Among them emulsion polymerization method is widely used in drug delivery.

8. **Polymerization techniques:**

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as

- a. Normal polymerization
 - b. Interfacial polymerization
- (Both are carried out in liquid phase)

a. **Normal polymerization:**

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

b. **Interfacial polymerization:**

Involves reaction of various monomers at the interface between the 2 immiscible liquid phases to form a film of polymer that essentially envelopes the dispersed phase. In this 2 reacting monomers are employed one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. Monomer present in either phases diffuse rapidly & polymerize rapidly at the interface. If the polymer is soluble in the droplet it will lead to the formation of monolithic type of the carrier on the other hand if polymer is insoluble in the monomer droplet, the formed carrier is of

capsular (reservoir) type. The degree of polymerization can be controlled by the reactivity of monomer chosen, their concentration, and composition of the vehicle of either phases and by the temperature of the system. The particle size can be controlled by controlling the droplets or globule size of the disperse phase. The polymerization reaction can be controlled by maintaining the concentration of the monomers, which can be achieved by the addition of an excess of the continuous phase.

9. Hot Melt Microencapsulation:

The polymer is first melted and then mixed acid solid drug particle or liquid drugs. This mixture is suspended in an immiscible solvent and heated to 50C above the melting point of the polymer under continuous stirring. The emulsion is then cooled below the melting point until the droplets solidify.

Ideal microspheres should have: ⁰¹

The material utilized for the preparation of microspheres should have the following properties

- ✓ Longer duration of action
- ✓ Provide protection of drug
- ✓ Sterilizability
- ✓ Water solubility
- ✓ Toxicity
- ✓ Water dispersability
- ✓ Relative stability
- ✓ Bioresorbability

Mechanism of Drug Release of Microspheres: ⁰¹

Different release mechanisms of encapsulated material provide controlled, sustained or targeted release of core material. Generally there are three different mechanisms by which the core material is released from a microcapsule-mechanical rupture of the capsule wall dissolution or melting of the wall and diffusion through the wall less common release mechanisms include ablation (slow erosion of shell) and biodegradation. Drug release from the microsphere occurs by general mechanism including diffusion, polymer degradation, and hydrolysis/erosion.

1. Diffusion:

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

2. Erosion:

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as the water penetrates within it leading to the plasticization of the matrix.

Evaluation parameters of Microspheres: ⁰¹

1. Particle size and shape:

Light microscopy (LM) provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. Scanning electron microscopy (SEM) allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems.

2. Attenuated total reflectance FT-IR Spectroscopy:

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring attenuated total reflectance (ATR). The ATRFT-IR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

3. Density determination:

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the density of the microsphere carrier is determined.

4. Isoelectric point:

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined.

5. Entrapment efficiency:

Microspheres containing of drug (5mg) were crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr., and was filtered then assayed by UV-Vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

$$\%DEE = \frac{\text{Actual Value}}{\text{Theoretical value}} \times 100$$

6. Swelling index:

This technique was used for Characterization of microspheres were performed with swelling index technique Different solution (100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37°C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.

7. Angle of contact:

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water interface. The angle of contact is measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200°C within a minute of deposition of microspheres.

8. Modified Keshary Chien Cell:

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 37°C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.

9. Dissolution apparatus:

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements, paddle 25, 26 and 27 and basket 28 and 29. Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

10. Animal models:

Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the esophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn and analyzed.

11. Stability studies:

By placing the microspheres in screw capped glass container and stored them at following conditions

- a. Ambient humid condition
- b. Room temperature (27+/-2 0C)
- c. Oven temperature (40+/-2 0C)
- d. Refrigerator (5 0C -80C).

It was carried out of a 60 days and the drug content of the microsphere was analysed.

Applications: ⁰¹

1. **Microspheres in vaccine delivery:**

The prerequisite of a vaccine is protection against the microorganism or its toxic product. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines.

2. **Topical porous microspheres:**

These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders.

3. **Targeting using micro particulate carriers:**

The concept of targeting, i.e. site specific drug delivery is a well-established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors.

4. **Surface modified microspheres:**

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance.

5. **Chemoembolization:**

Chemoembolization is an endovascular therapy, which involves the selective arterial embolization of a tumor together with simultaneous or subsequent local delivery the chemotherapeutic agent.

6. **Imaging:**

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labeled microspheres.

7. **Monoclonal antibodies mediated microspheres:**

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is a method used to achieve selective targeting to the specific sites.

8. **Sustained drug delivery:**

By encapsulating a drug in a polymer matrix, which limits access of the biological fluid into the drug until the time of degradation, microparticles maintain the blood level of the drug within a therapeutic window for a prolonged period. Toxic side effects can be improved by reducing the frequency of administration. E.g. A novel sustained release microspheres of Glipizide are quite beneficial for diabetic patient.

9. **Controlled drug delivery:**

Here, the drug is delivered at a predetermined rate, locally or systemically for a specified period of time. Depot formulation of short acting peptide have been successfully developed using microparticle technology. E.g. leuporelin acetate and triptoreline, both are luteinizing hormone releasing hormone agonists.

10. **Local drug delivery:**

Subcutaneously or intramuscularly applied microparticles can maintain a therapeutically effective concentration at the site of action for a desirable duration. The local delivery system obviates systemic

drug administration for local therapeutic effects and can reduce the related systemic side effects. It is proven beneficial for delivery of local anesthetics.

11. Ophthalmic Drug Delivery:

Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow.

12. Pulsatile drug delivery

While burst and pulsatile release is not considered for sustained delivery application, their release pattern proves to be useful for delivery of antibiotics and vaccines. Pulsatile release of antibiotics can alleviate evolution of the bacterial resistance. In the vaccine delivery, initial burst followed by delayed release pulsed can mimic an initial and boost injection respectively. Potential application of this drug delivery system is replacement of therapeutic agents, gene therapy, and in use of vaccine for treating AIDS, tumors, cancer, and diabetes. The spheres are engineered to stick tightly to and even penetrate linings in the GIT before transferring their contents over time into circulatory system. Based on this novel drug delivery technique, Quinidine gluconate CR tablets are used for treating and preventing abnormal heart rhythm. Glucotrol (Glipizide SR) is an antidiabetic drug used to control high blood sugar levels.

13. Gene delivery:

Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Polymer has been used as a carrier of DNA for gene delivery applications. Also, polymer could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract.

14. Oral drug delivery:

The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications.

15. Nasal drug delivery:

The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Polymer based drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride.

16. Buccal drug delivery:

Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Buccal tablets based on chitosan microspheres

containing chlorhexidine diacetate gives prolonged release of the drug in the buccal cavity improving the antimicrobial activity of the drug.

17. Vaginal drug delivery:

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, an imidazole derivative, is widely used for the treatment of mycotic infections of the genitourinary tract. By introducing thiol groups, the mucoadhesive properties of the polymer are strongly improved and this is found to increase the residence time of the vaginal mucosa tissue (26 times longer than the corresponding unmodified polymer), guaranteeing a controlled drug release in the treatment of mycotic infections.

18. Transdermal drug delivery:

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Chitosan-alginate polyelectrolyte complex has been prepared in-situ in beads and microspheres for potential applications in packaging, controlled release systems and wound dressings.

19. Other application of microspheres:

- a. For Taste and odour masking
- b. To delay the volatilization
- c. For Separation of incompatible substances
- d. For Improvement of flow properties of powders
- e. To Increase the stability of the drug against the external conditions
- f. For Safe handling of toxic substances
- g. To Improve the solubility of water insoluble substances by incorporating dispersion of such material in aqueous media
- h. To reduce the dose dumping potential compared to large implantable devices
- i. For conversion of oils and other liquids to solids for ease of handling

Conclusion:

It has been observed that the floating microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of detection of bimolecular interactions and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for targeting. So in future microspheres will have an important role to play in the advancement of medical field. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *In vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body. The main central idea of this paper is to create excites in researchers and scholars about "Floating microspheres: A novel Gastro Retentive Drug Delivery System."

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