



A review on Microspheres: Types, Formulation Methods, Characterization and Application

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Abstract: Drug distribution management has progressed significantly over the last three decades and has become an important part of pharmaceutical development. Conventional medicines have some limitations, such as the need to frequently check the plasma concentration of drugs, especially for drugs with short half-lives. Frequent use of the drug causes deterioration in patient compliance and changes in plasma concentration. These challenges can be addressed by developing new drugs, particularly controlled drug delivery, that can keep plasma drug stable by slowly releasing the drug over a longer period of time. Controlling drug distribution can also improve the bioavailability of drugs, thus improving treatment and patient compliance. There are many methods for controlled delivery, including liposomes, liposomes, ethosomes, phytosomes, microemulsions, and microspheres. Among these formulations, microspheres are particularly good because they slow the release of drugs from polymer matrices, and the polymers used are mostly biodegradable and have no side effects. For this reason, microspheres are used in many medical fields such as oncology, radiology, gynecology, cardiology, pulmonology, diabetes and medicine. This review article summarizes the different types of microspheres and current advances in their design. Additionally, microspheres can be analyzed and functionalized using a variety of methods.

Keywords: Controlled drug delivery system, Improved systemic bioavailability, Constant drug plasma level.

Introduction

When taking medication, the oral route is the most recommended method. Nevertheless, many medications' therapeutic potential is limited by their brief half-lives in circulation and limited absorption through a certain intestinal segment. In many circumstances, pharmacokinetic limitations like this necessitate repeated pharmaceutical dosages to achieve therapeutic efficacy. Controlled, site-specific medication release is a logical strategy to boost bioavailability and optimize pharmacokinetic and pharmacodynamic characteristics. Microspheres are small spherical particles, with diameters of 1 μm to 1000 μm . They are spherical free-flowing particles consisting of proteins or synthetic polymers that are biodegradable. There are two types of microspheres; microcapsules and micromatrices. Microcapsules are those in which an entrapped substance is distinctly surrounded by a distinct capsule wall. and micro matrices in which entrapped substances are dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural as well as synthetic materials. Microspheres play an important role in improving bioavailability of conventional drugs and minimizing side effects. Microencapsulation is done to modify and retard the drug release.[1-4] Due to the small particle size, it is widely distributed throughout the GIT which helps in improving the drug absorption and reduces the side effects.[5]

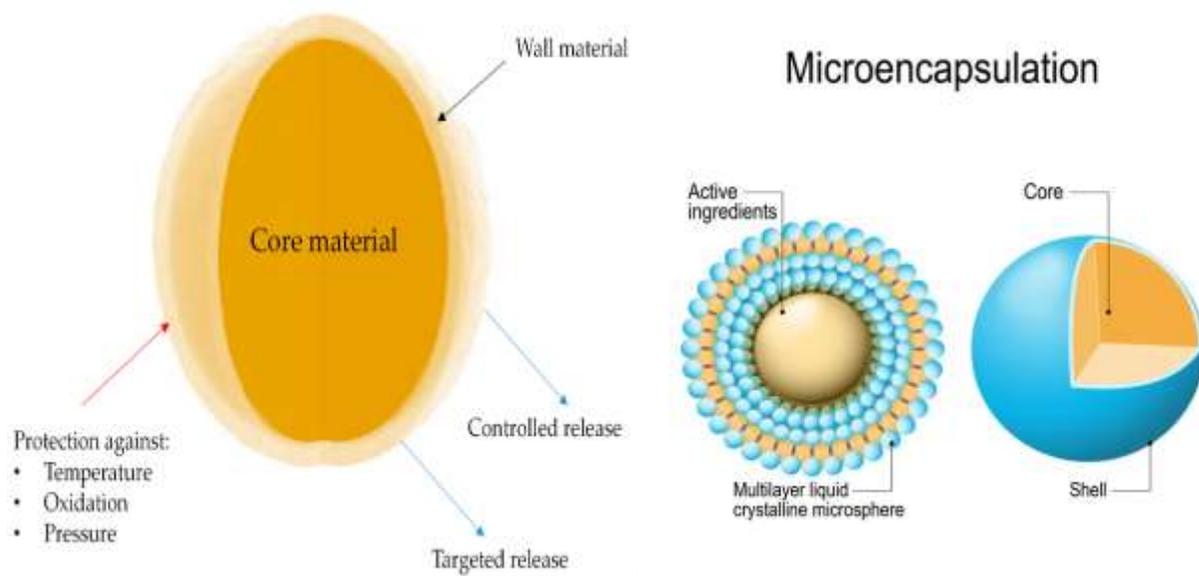


Fig.1 Structure of Microsphere

ADVANTAGES

1. The therapeutic effect of microspheres is continuous and long-lasting.
2. It Lowers the frequency of dose, which increases patient compliance.
3. Because of their smaller size and spherical form, they could be injected into the body.
4. More effective use of medications will increase their absorption and lessen the frequency or severity of side effects.
5. The shape of microspheres permits a regulated degree of diversity in medication release and breakdown. [6]

LIMITATION

The limitations were found to be as follows:

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form can differ from a variety of factors like food and the rate of transit through the gut.
3. Differences in the rate of release from one dose to another dose.
4. Controlled-release formulations usually contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
5. Dosage forms of such types should not be crushed into particles or chewed [6]

APPLICATIONS IN DRUG DELIVERY SYSTEMS[7]

1. Ophthalmic drug delivery
2. Gene delivery
3. Oral drug delivery
4. Nasal drug delivery
5. Intra-tumoral and local drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery
8. Transdermal drug delivery
9. Peroral drug delivery
10. Colonic drug delivery
11. Vaginal drug delivery
12. multi particulate delivery system

TYPES OF MICROSPHERES: [8]

1. Bio-adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres
 - i) Biodegradable polymeric microspheres
 - ii) Synthetic polymeric microspheres

1. Bio-adhesive microspheres:

Adhesion can be defined as the sticking of the drug to the membrane by using the sticking property of the water-soluble polymers. Adhesion of drug delivery devices to the membrane of mucous such as buccal, ocular, rectal, nasal etc. is called as Bio-adhesion. These kinds of microspheres exhibit a prolonged residence time at the application site causing intimate contact with the absorption site and giving better therapeutic action.[9,10]

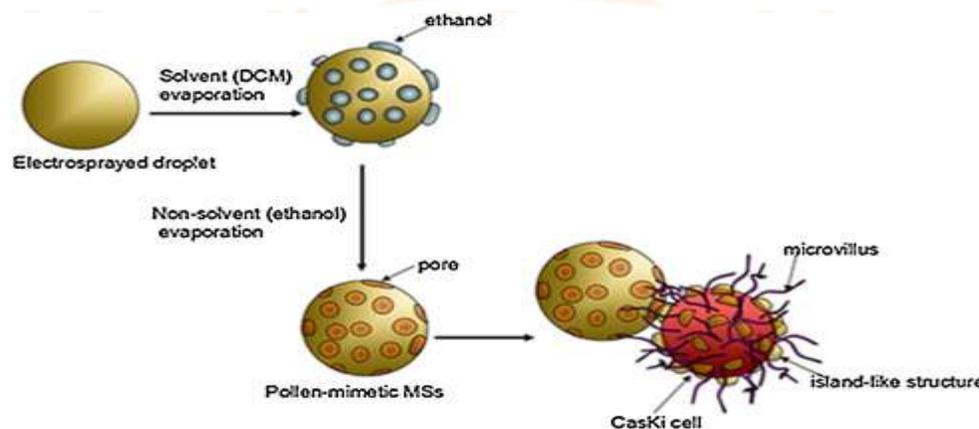


Fig.2 Bio-adhesive microspheres

2. Magnetic microspheres:

Such kind of delivery system is very much important which localises the drug to the disease or target site. This larger amount of free circulating drug can be substituted by a smaller amount of magnetically targeted drug. Magnetic carriers receive the magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres such as chitosan, dextran etc.

(i) **Therapeutic magnetic microspheres** are used to deliver chemotherapeutic agents to liver tumors. Drugs like proteins and peptides are also targeted through this system. [11,12]

(ii) **Diagnostic microspheres**: these microspheres are used for imaging liver metastasis and also can be used to distinguish between bowel loops and other abdominal structures by forming nano-size particles of superparamagnetic iron oxides.

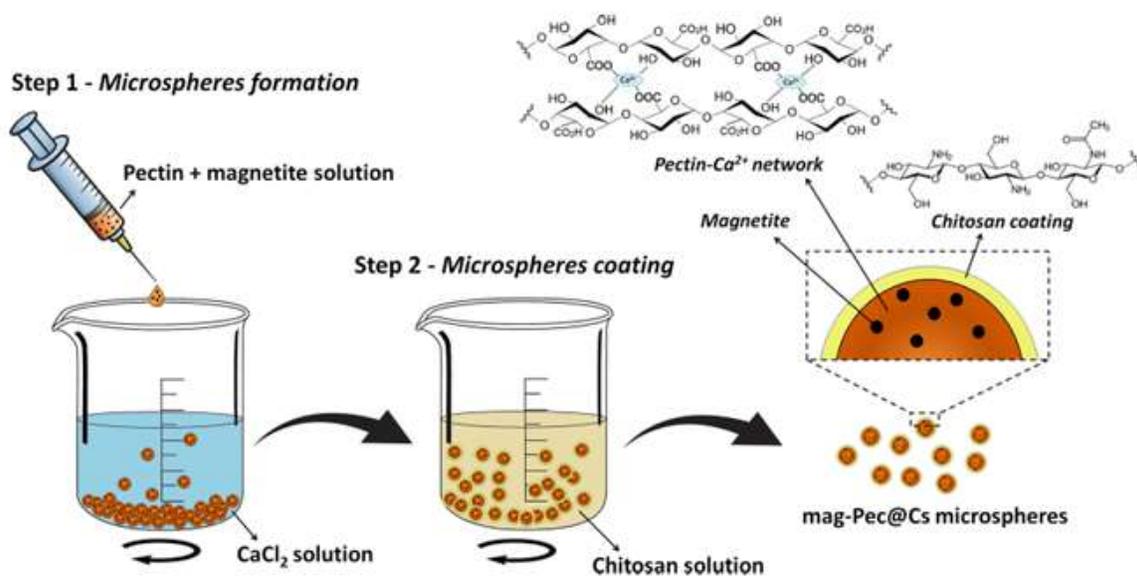


Fig.3 Formulation of magnetic microspheres

3. Floating microspheres

In these microspheres, the bulk density is less than the gastric fluid and thus remains buoyant in the stomach without altering the gastric emptying rate. The drug is released at the desired slow rate. If the system is floating on the gastric content, it increases gastric residence and increases fluctuation in the plasma concentration. Moreover, it is also reducing the chances of striking and dose dumping. Another way is producing a prolonged therapeutic effect and therefore reducing the dosing frequencies. [13,14]

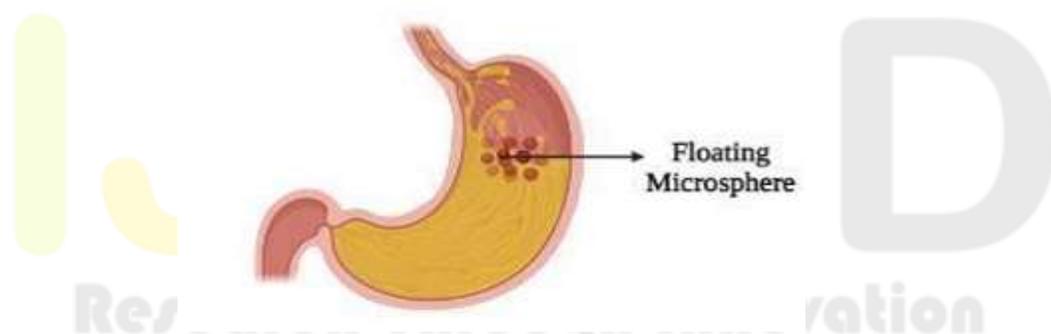


Fig.4 Floating Microspheres

4. Polymeric Microspheres

Various types of polymers such as sodium alginate and PMMA are used to bind and encapsulate the drug in a microsphere shape with controlled release [15]. The different types of polymeric microspheres are as follows:

i) Biodegradable polymeric microspheres.

Natural polymers such as starch, Albumin, Collagen and Gelatin, and Alginate are used as a concept that they are biodegradable, biocompatible, and also act as bio-adhesives in nature. These polymers prolong the residence time

when come in contact with mucous membranes due to their high degree of swelling property with an aqueous medium, leading to gel formation. [16,17]

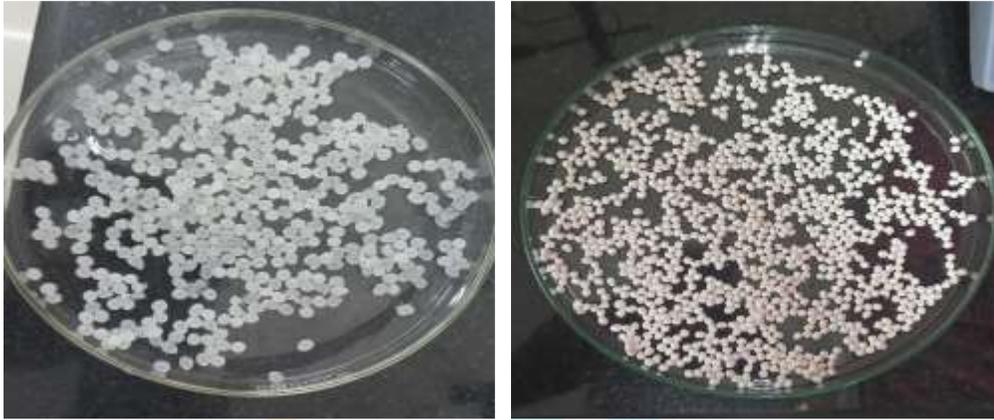


Fig.5 Sodium Alginate Microspheres

ii) Synthetic polymeric microspheres

These are mostly used in clinical applications and are also being used as bulking agents, fillers, embolic particles drug delivery vehicles etc. and proved to be safe and biocompatible but the disadvantage of such kinds of microspheres tend to migrate away from injection sites and results to potential risk, embolism, further leading to organ damage.[18-21]

4. Radioactive microspheres

These microspheres are used in Radioembolization therapy in which microspheres having sizes 10-30 μm are larger than capillaries. They are injected into arteries which leads to tumors of interest. These radioactive microspheres deliver high radiation doses to targeted areas without any damage to the normal tissues. Different types of radioactive microspheres are being used such as α emitters, β emitters, γ emitters. [17]

Polymers used in microsphere formulation[22-25]

Microspheres usually use polymers.

1. Natural polymers
2. Synthetic Polymers

1. Natural polymers

- (i) **Carbohydrates:** Agarose, Carrageenan, Chitosan, Starch
- (ii) **Proteins:** Albumin, Collagen and Gelatin
- (iii) **Chemically modified carbohydrates:** Poly dextran, Poly starch

2. Synthetic polymers

- i) **Biodegradable polymers:** Lactides, Glycosides & their co-polymers, Poly anhydrides, Poly alkyl cyanoacrylates
- ii) **Non-biodegradable polymers:** Polymethyl methacrylate (PMMA), Glycidyl methacrylate, Acrolein, Epoxy polymers

The multivalent ions are necessary for the formulation of beads:

Cations: Calcium (Ca^{+2}) Potassium (K^{+1}), F, Barium (Ba^{+2}), Magnesium (Mg^{+2}), Aluminum (Al^{+3}), Zinc (Zn^{+2}),

Anions: Tripolyphosphate (TPP⁻), sodium sulfate.

Common polymers utilized in beads technology:

1. Sodium Alginate
2. Chitosan
3. Carboxy Methyl Cellulose

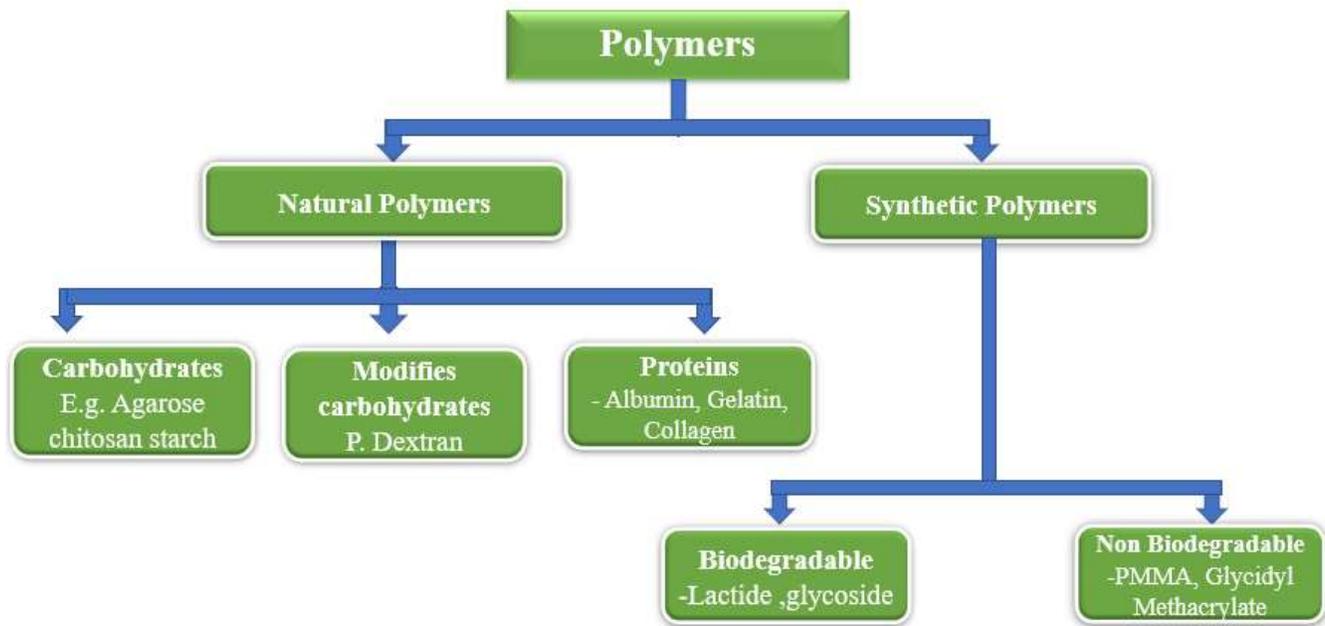


Fig. 6 Types of polymers used in microsphere formulation

Mechanism of microspheres

The majority of drug delivery via microparticles inhibits the formation of a matrix-like internal solid dispersion morphology structure. The drug can be insoluble in the matrix of polymer, and it is released through erosion. First, water diffuses into the matrix, dissolving the resulting near the device's surface. The resulting osmotic pressure gets alleviated by forming a channel to the surface and releasing a predetermined amount of drug in the initial drug burst.

Drug release from the microspheres occurs by a general mechanism including

- Dissolution,
- Diffusion,
- Polymer degradation,
- Hydrolysis/erosion. [26]

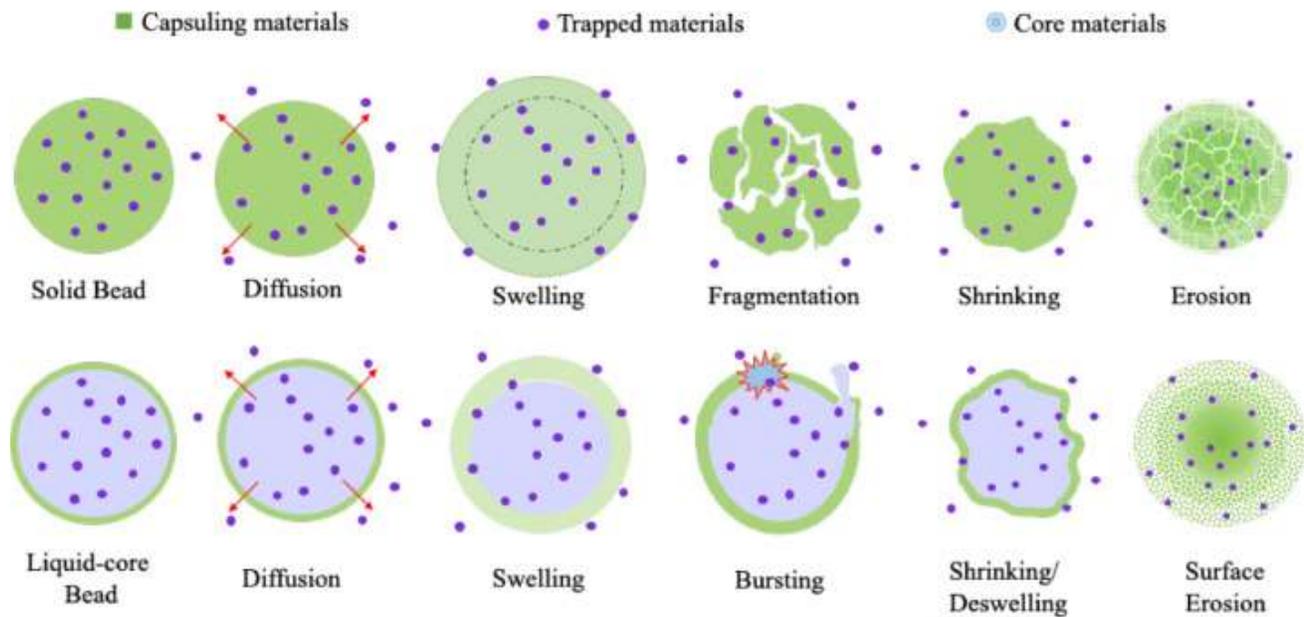


Fig.7 Drug release mechanism from microspheres

Method of preparation of microspheres[27]

1. Solvent evaporation techniques
 - a. Single emulsion techniques
 - b. Double emulsion techniques
2. Polymerization
 - a. Normal polymerization
 - b. Interfacial polymerization
3. Phase separation coacervation technique
4. Spray drying
5. Emulsion crosslinking method
6. Ion gelation method

1.Solvent evaporation techniques

a) Single emulsion technique

The micro particulate carriers of the natural polymers i.e. proteins and carbohydrates are prepared by this technique. An aqueous medium is used to dissolve these Natural polymers which is followed by dispersion in a non-aqueous medium such as oil. In the next step, the cross-linking of dispersed globules is carried out. The cross-linking can be gained by heat or by using chemical cross-linkers. The chemical cross-linking agents being used are glutaraldehyde, formaldehyde, and acid chloride. Heat denaturation is not considered suitable for thermolabile substances. Chemical cross-linking has the disadvantage of excessive exposure of active ingredients to the chemicals if added at the time of preparation and then subjected to centrifugation, washing, and separation, Thenature of the surfactants being used to stabilize the emulsion phases can be greatly influenced by the size, size distribution, surface morphology and loading drug release, and bio performance of thefinal multi particulate product.[28]

b) Double emulsion technique:

This method of microsphere preparation involves the formulation of multiple emulsions or double emulsions of type w/o/wand it is best suited to water-soluble drugs, peptides, proteins and vaccines. This method can be carried out

with both natural as well as synthetic polymers. The aqueous protein solution is dispersed in the lipophilic organic continuous phase or dispersion medium. This protein solution may contain the active constituents. [29]

2. Polymerization techniques

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

Normal polymerization It is followed by different techniques such 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 the polymerization. The polymer so obtained can be moulded as microspheres. Drug loading can be done during the

process of polymerization. Suspension polymerization is also called as bead or pearl polymerization. In this case, the monomer or mixture of monomers is heated as the droplets disperse in an ongoing aqueous phase. The droplets can also carry an initiator and other additives. Emulsion polymerization differs from suspension polymerization due to the presence of initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has the advantage of formation of pure polymers. [30]

Interfacial polymerization

This method involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. [30]

3. Phase separation coacervation technique:

This process is based on the principle of decreasing the solubility of the polymer in the organic phase which affects the formation of polymer-rich phase called the coacervates. In this method, drug particles are dispersed in a solution of polymer and an incompatible polymer is added to the system which makes the first polymer for the phase separation. [28]

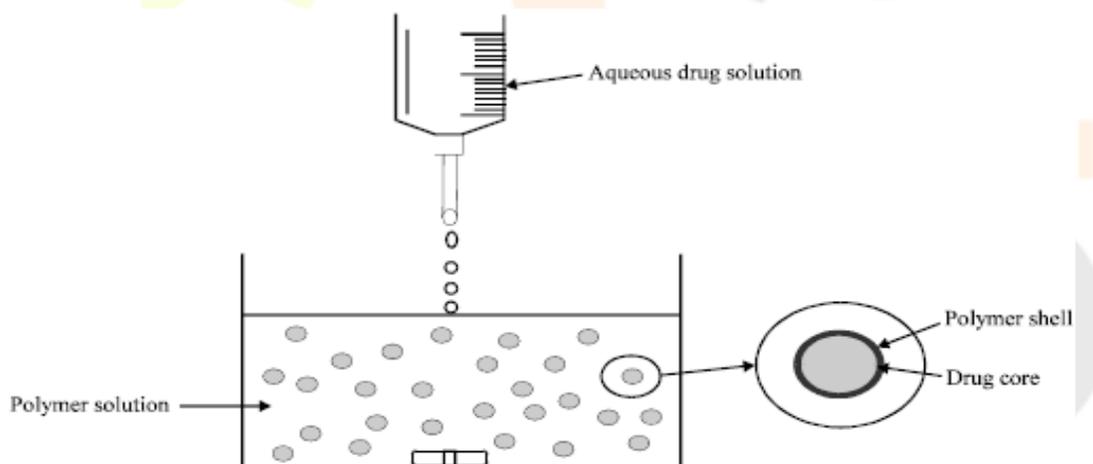


Fig. 8 Phase separation coacervation technique

4. Spray Drying Technique:

This technique was used to prepare a polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of the solvent. Organic solutions of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and then sprayed in different experimental conditions resulting in drug-loaded microspheres. This is a rapid method but can lead to loss the crystallinity due to the fast-drying process. (31)

5. Emulsion Cross Linking Method:

In this method, the aqueous gelatin was previously heated for 1 hr at 40°C and then the drug was dissolved in that aqueous gelatin solution. The solution was added dropwise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35°C, resulting in w/o emulsion then further stirring was done for 10 min at 150°C. Thus the produced microspheres were washed three times with acetone and isopropyl alcohol respectively, which then air dried and dispersed in 5 mL of aqueous glutaraldehyde-saturated toluene solution at room temperature for 3 hrs for cross-linking and then it was treated with 100 mL of 10 mM glycine solution containing 0.1% w/v of tween 80 at 37°C for 10 min to block unreacted glutaraldehyde. Gelatin A microspheres are one of the examples of this technique. [31]

6. Ionic Gelation Method

This technique is used for preparing the Alginate/chitosan particulate system for different drugs in controlled release. Different % (w/v) of drugs get added to aqueous solution of sodium alginate. To get the complete solution stirring is continued and after that, it is added dropwise to a solution containing Ca⁺ and chitosan solution in acetic acid. Microspheres formed by this will be kept in the original solution for 6 hrs & 24 hrs for internal gelification followed by filtration for separation. The complete release will be obtained at pH 7.4 but the drug did not release in acidic pH. [31]

Evaluation of Microspheres: Physicochemical characterization

The characterization of the microspheres is an important phenomenon which helps to design a suitable carrier for the delivery of proteins, drugs or antigens. These microspheres have different microstructures. These microstructures determine the release and the stability of the microspheres [32].

1. Particle size and shape: The most used procedures to visualize microspheres are conventional Light Microscopy (LM) and Scanning Electron Microscopy (SEM). Both techniques can be used to determine the shape and outer structure of these microspheres. Light Microscopy (LM) provides control over coating parameters in the case of double-walled microspheres. The microsphere structures may be visualized before and after coating and the change can be measured by microscope. SEM provides higher resolution in comparison to the LM [33]. Scanning Electron Microscopy (SEM) allows investigations of the surface of the microsphere and after particles are cross-sectioned, it can also be used for the investigation of double-walled systems. Confocal fluorescence microscopy is used for the structure characterization of multiple-walled microspheres [34]. Laser light scattering and multi-size coulter counter other than instrumental methods can be used for the characterization of the size, shape and morphology of the microspheres.

2. Density determination: The density of the microspheres can be measured by using a device called a multi-volume pycnometer. An accurately weighed sample in a cup is then placed into the multi-volume pycnometer. Helium is introduced at a constant pressure in the chamber and it is allowed to expand. This expansion leads to a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressures are noted down. From two pressure readings, the volume and thus the density of the microsphere carrier is determined [35].

3. Isoelectric point: The microelectrophoresis is an apparatus that is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The average velocity at different pH values ranging from 3 to 10 is calculated by measuring the time of movement of particles over a distance of 1 mm. By using this data, the electrical mobility of the particle can also be determined. The electrophoretic mobility may be related to the surface-contained charge, ionisable behaviour or ion absorption nature of the microspheres.

4. Angle of contact: The wetting property of a microparticulate carrier is ascertained by measuring the angle of contact. This finds out the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solids and it gets affected by the presence of the adsorbed component. A solid/air/water interface is used to measure the Angle of contact. The advancing and receding angle of contact is measured by placing a droplet in a circular cell mounted above the objective of the inverted microscope. The contact angle is measured at 20°C within a minute of deposition of microspheres [36].

5. Electron spectroscopy for chemical analysis: The surface chemistry of the microspheres can be determined using Electron Spectroscopy for Chemical Analysis (ESCA). The technique of Electron Spectroscopy for Chemical Analysis (ESCA) makes it possible to ascertain the surface's atomic composition. The spectra obtained by using ESCA can be used to determine the surface degradation of the biodegradable microspheres.

6. Fourier transform-infrared spectroscopy: the degradation of the polymeric matrix of the carrier system is determined by using the FT-IR. The surface of the microspheres is investigated by measuring Alternated Total Reflectance (ATR). The IR beam that passes through the ATR cell gets reflected many times through the sample to provide IR spectra mainly of surface material. The ATR-FTIR provides information about the surface composition of the microspheres depending on manufacturing procedures and conditions [37].

7. Swelling Index

To calculate the swelling index, measure the extent to which microspheres expand when placed in a specific solvent. Assess the equilibrium swelling degree by allowing 5 mg of dried microspheres to swell overnight in a measuring cylinder containing 5 ml of buffer solution [38]. Use the provided formula to compute the swelling index.

$$\text{Swelling index} = \frac{w_f - w_o}{w_o} \times 10$$

8. Entrapment efficiency: The capture efficiency of the microspheres or the per cent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per the monograph requirement [38]. The per cent encapsulation efficiency is calculated using the following equation:

$$\%EE = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

9. The percentage yield

The percentage yield is calculated by dividing the total weight of the medication and polymer used to prepare each batch by the weight of the microspheres obtained from that batch, and then multiplying the result by 100. [38]

$$\% \text{ Yield} = \frac{\text{Practical yield}}{\text{theoretical yield}} \times 100$$

10. Drug Loading Efficiency

Drug loading is the amount of drug loaded per unit nanoparticle weight, indicating the percentage of nanoparticle weight which is attached to the encapsulated product. Drug loading (%) can be determined by the total amount of drug entrapped, divided by the total weight of nanoparticles. In the delivery of drugs, yield is given as a percentage which represents the amount of drug delivered per quantity. [38]

$$\%LC = \frac{\text{Actual drug content}}{\text{Total weight of microsphere}} \times 100$$

In Vivo Methods

In vivo methods are utilized to study the permeability of intact mucosa, taking advantage of the biological responses of the organism, either locally or systemically. Historically, the simplest studies of mucosal layer permeability involved observing the systemic pharmacological effects after drug ingestion or absorption through the oral mucosa. Currently, the most common techniques involve the use of animal models, buccal absorption tests, and corneal perfusion chambers to study drug permeability. [39]

1. Animal Models

Animal models are used to screen a series of compounds to explore the mechanisms and effectiveness of permeation enhancers or to evaluate different formulations. Various animals such as dogs, rats, rabbits, cats, hamsters, pigs, and sheep are commonly used. The procedure includes anaesthetizing the animal and administering the dosage form to be studied. For example, in rats, the esophagus is ligated to prevent absorption pathways other than the oral mucosal layer. The absorption rate is then determined by withdrawing blood samples at different intervals and analyzing them. [39]

2. Buccal Absorption Test

Known for its simplicity and reliability, the buccal absorption test measures the extent of drug loss in the oral cavity using single or multi-component drug mixtures. This method determines the structure, contact time, pH, and initial drug concentration of the solution when the drug is held in the oral cavity. [40]

3. Corneal Perfusion Chambers

The corneal perfusion chamber method is very useful in developing and accessing ophthalmic drugs. This method involves designing and testing a modified perfusion chamber suitable for the topical application of drugs isolated to corneoscleral preparations, allowing continuous monitoring of endothelial cell function. The chamber, made from polycarbonate and stainless steel, clamps corneas in a horizontal plane, making it suitable for topical drug delivery. Endothelial cell function is assessed using ultrasonic pachymetry and specular microscopy during perfusion, while epithelial barrier function is evaluated by measuring fluorescein penetration. Leakage is assessed by measuring the penetration of large proteins, and tissue architecture is examined using conventional histology after perfusion. [41]

In Vitro Methods

1. Beaker Method

In this method, the dosage form is adhered to the bottom of a beaker containing the medium, which is uniformly stirred using an overhead stirrer. The medium volume ranges from 50 to 500 ml, and the stirrer speed varies from 60 to 300 rpm. Samples are withdrawn at intervals to determine the amount of drug dissolved in the medium. [42]

2. Interface Diffusion System

Dearden and Tomlinson developed the interface diffusion system with four compartments. Compartment A represents the oral cavity and contains the drug in a buffer. Compartment B, representing the buccal membrane, contains 1-octanol. Compartment C, representing body fluids, contains 0.2 M HCl. Compartment D, representing protein binding, also contains 1-octanol. Before use, the aqueous phase and 1-octanol are saturated with each other. Samples are withdrawn and returned to compartment A with a syringe. This system allows the determination of drug dissolution in different body compartments by analyzing samples from all four compartments. [39]

3. Modified KesharyChien cell method

It utilizes equipment specifically designed for laboratory use. This setup includes a KesharyChien cell containing 50 cc of distilled water and a dissolving medium maintained at 37 °C. Within a glass tube, which has a #10 sieve at the bottom and moves back and forth in the medium at a rate of 30 strokes per minute, a TMDDS (Trans Membrane Drug Delivery System) is placed. [43]

4. Dissolution apparatus method

The paddle and basket, both rotating components, have been employed in standard USP or BP dissolution apparatuses to assess in vitro release characteristics. The dissolution medium used in the study varies between 100 to 500 ml, with a rotational speed ranging from 50 to 100 rpm. [43]

Applications of microspheres as drug delivery system

1. Microspheres in Vaccine Delivery

A vaccine's primary requirement is to provide protection against a microorganism or its toxic product. An ideal vaccine must meet the criteria of efficacy, safety, ease of administration, and cost-effectiveness. Ensuring safety and minimizing adverse reactions is a complex issue. The safety aspect and the level of antibody response production are closely tied to the mode of administration. Biodegradable delivery systems for vaccines administered via the parenteral route can address the limitations of traditional vaccines. Interest in parenteral carriers (subcutaneous, Intramuscular, Intradermal) is due to their specific advantages, including:

1. Enhanced antigenicity through adjuvant action,
2. Modulation of antigen release
3. Stabilization of the antigen. [39]

Biodegradable microspheres have been employed for vaccine delivery via the parenteral route, offering advantages such as sustained release and targeted delivery. Various vaccines, including those for tetanus and diphtheria, have been encapsulated in polymeric microspheres. [44]

2. Targeting Using Microparticulate Carriers

The concept of targeting, or site-specific drug delivery, is a well-established principle that is receiving significant attention. The therapeutic effectiveness of a drug depends on its ability to reach and specifically interact with its target receptors. Effective drug action through a carrier system relies on the drug's capacity to leave the reservoir in a consistent, efficient, and specific manner. Positioning the particles in specific anatomical compartments ensures their retention, either due to the physical characteristics of the environment or the biophysical interactions between the particles and the cellular content of the target tissue. [39]

3. Oral Drug Delivery:

Microspheres containing polymers can form films, making them suitable for creating film dosage forms as an alternative to traditional pharmaceutical tablets. Their pH sensitivity and the reactivity of primary amine groups enhance their suitability for oral drug delivery applications, such as with Chitosan and Gelatin. [45]

4. Gene Delivery

Microspheres can serve as effective oral gene carriers due to their adhesive and transport properties within the gastrointestinal tract. Examples include Chitosan, Gelatin, viral vectors, cationic liposomes, and polycation complexes. This technology is used in gene therapy with DNA plasmids and in the delivery of insulin. Additionally, it is advantageous for vaccine delivery, as vaccines must protect against microorganisms or their toxic products.

Biodegradable delivery systems for vaccines administered via the parenteral route can address the limitations of conventional vaccines. Several parenteral vaccines, including those for tetanus and diphtheria, have been encapsulated in biodegradable polymeric microspheres. [45]

5.Nasal Drug Delivery

Polymer-based drug delivery systems, including microspheres, liposomes, and gels, exhibit favourable bio-adhesive properties and readily swell upon contact with the nasal mucosa. This enhances drug bioavailability and prolongs residence time in the nasal route. This route offers advantages such as rapid onset of action and avoidance of first-pass metabolism. Examples include starch, dextran, albumin, and combinations like chitosan with gelatin.

6.Intra-tumoral and Local Drug Delivery

Polymer films are fabricated to deliver drugs like paclitaxel directly to tumor sites in therapeutically relevant concentrations. This approach shows promise for controlled drug delivery, including in the oral cavity. Materials such as gelatin, PLGA, and chitosan are utilized.

7.Gastrointestinal Drug Delivery

Polymer granules with internal cavities, formed through deacidification, exhibit buoyancy in acidic and neutral media. These polymers enable controlled drug release. Examples include Eudragit, ethyl cellulose combined with carbopol, BSA, and gelatin.

8.Transdermal Drug Delivery

Polymers with good film-forming properties, such as chitosan, alginate, and PLGA, are utilized for transdermal drug delivery. Drug release from these devices is influenced by factors like membrane thickness and cross-linking of the film.

9.Monoclonal Antibodies

Monoclonal antibodies or targeting microspheres are biologically immune microspheres used for selective targeting to specific body organ sites. They bind specifically to certain molecules, facilitating absorption through non-specific or specific adsorption, direct coupling, or coupling via reagents.

10.Imaging

The size of microspheres is critical in determining the imaging of specific sites targeted using pre-labelled microspheres with radioactivity. When microspheres are injected intravenously, they often become trapped in the lungs, particularly when injected aside from the portal vein. This process is specifically utilized for scintigraphic imaging of tumors masses in the lungs using microspheres made from human serum albumin.

11. Topical Porous Microspheres,

These are also known as micro-sponges, are porous microspheres with interconnected voids ranging in size from 5 to 300µm. These structures have the capacity to encapsulate various active ingredients such as emollients, fragrances, and essential oils for topical application.

12.Medical Application

Extended-release of proteins, peptides, and hormones.

Passive targeting of leaky tumor vessels and active targeting of tumor cells and antigens via the parenteral route.

Magnetic microspheres can be utilized for stem cell extraction and bone marrow purging.

Used in various diagnostic tests for infectious diseases such as bacterial, viral, and fungal infections.

13.Radioactive Application

Beneficial for embolization of liver and spleen tumors, as well as for radio synovectomy, local radiotherapy, arthritis treatment, and imaging of the liver, bone marrow, and thrombus in deep vein thrombosis.

14. Other Applications

Fluorescent microspheres are employed in membrane-based technologies, flow cytometry, cell biology, and fluorescent-linked immunosorbent assays.

Yttrium-90 can be used for primary treatment of carcinoma and pre-transplant management of hepatocellular carcinoma with promising results.

15. Colonic Drug Delivery

Polymers like chitosan have been utilized for specific delivery of insulin to the colon.

16. Vaginal Drug Delivery

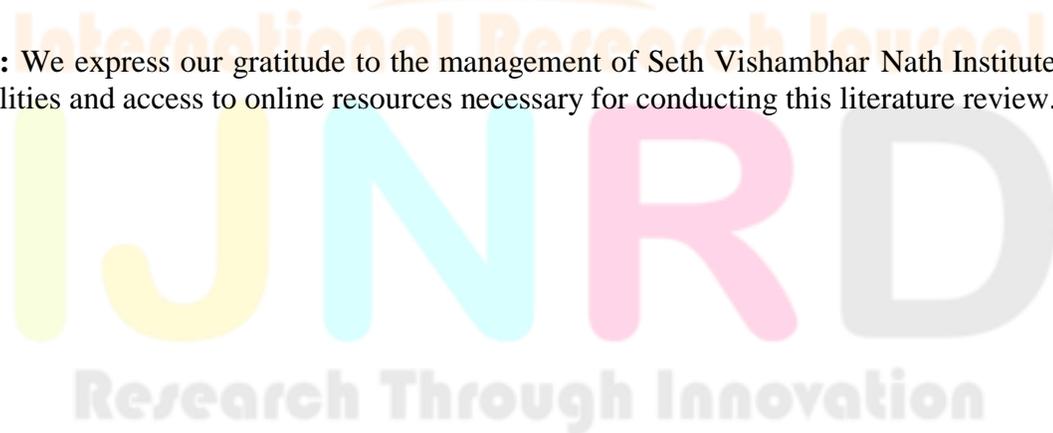
Polymers modified with thioglycolic acid are widely used for treating mycotic infections of the genitourinary tract, including chitosan, gelatin, and PLGA. [46]

Conclusion

From this comprehensive review, it is evident that microspheres serve as a versatile and effective drug delivery system, offering various preparation methods and pharmaceutical applications. They facilitate the controlled delivery of medications in a precise manner, catering to diverse needs such as oral, targeted, sustained, topical, and even biotechnological applications like gene therapy. By continually advancing delivery technologies, microspheres promise significant therapeutic and commercial benefits, including improved safety profiles and reduced toxicity. Pharmaceutical companies are increasingly introducing innovative products to the market, demonstrating enhanced therapeutic responses compared to conventional delivery methods. The ongoing development of microsphere-based drug delivery technologies addresses challenges across pharmaceutical, biopharmaceutical, and pharmacokinetic domains, thereby fostering their widespread acceptance and utilization worldwide. Microspheres emerge as a superior choice in drug delivery systems, offering target specificity, enhanced patient compliance, and promising solutions for sustained and targeted drug delivery across various biological systems. Their versatility extends beyond drug delivery to encompass applications in imaging tumors, diagnosing biomolecular interactions, and contributing to cancer treatment, making them pivotal components in future advancements in drug delivery and healthcare.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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