International Journal of Basic & Clinical Pharmacology
*Anusha R et al. Int J Basic Clin Pharmacol. 2025 Mar;14(2):307-315*
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20250494

**Review Article**

# Formulation and characterization studies of microspheres

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**Received:** 03 December 2024
**Revised:** 19 January 2025
**Accepted:** 20 January 2025

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## ABSTRACT

In the current scenario of delivering therapeutic agents to the target site requires an efficient drug delivery carrier which can delivery the drug only on the site of action in a sustained and controlled manner among many such carriers microspheres fulfill all the parameters for a potent drug carrier. Microspheres are free flowing powders consists of proteins or synthetic polymers that are biodegradable in nature ranging between 1–1000-micron size. A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy an enhanced the therapeutic efficacy of given drug. Microspheres received much attention not only for prolonged release, but also targeted anticancer drugs. Microspheres can be manufactured by various type of material such as glass, polymers and ceramics microspheres. Microspheres are various types like bioadhesive microspheres, magnetic microspheres, floating microspheres, radioactive microspheres, polymeric microspheres are prepared by methods like spray drying, solvent evaporation, single emulsion, double emulsion, solvent extraction, quassi emulsion solvent diffusion. Microspheres will play a key role in novel drug delivery in the future by fusing together a variety of other strategies especially in diseased cells, diagnostics and act as supplements as miniature versions of diseased organ and tissues in the body.

**Keywords:** Microspheres, Types of microspheres, Method of preparation, Marketed drugs, Characterization and applications

## INTRODUCTION

The term microsphere refers to free-flowing spherical particles made up of medicament and polymer matrix. They are composed of synthetic polymers or proteins which are biodegradable in nature and have a particle size of less than 200µm.1These are tiny, spherical particles and typically having dimensions between 1 to 1000 µm. Microspheres sometimes referred to as microparticles.[2] There are two types of microspheres microcapsules and micromatrices. In micromatrices the entrapped material is distributed throughout the microsphere matrix. In microcapsules the entrapped material is enclosed by a discrete capsule wall.[3] Microspheres improve the drugs therapeutic efficacy and bioavailability, reduces toxicity and minimizes side effects.[4] Microspheres can be prepared by various materials such as natural and synthetic materials. It plays a crucial role in enhancing the absorption of traditional medicines and microencapsulation is a alter method to delay the release of medicine. Because of smaller particle size it broadly dispersed throughout the GIT and improves drug absorption.[5] The most convenient and preferable method is oral route of drug administration mainly frequent doses maintain steady plasma concentration and have low patient compliance.[6]

Some issues can overcome by controlled drug delivery. So, microspheres are one such method to mainly load the drug and used for targeted drug delivery.[7] The first microspheres were created in 1997 to support the long-term effects of medication and an alternative method for

traditional or quick release formulations.[8] These particles are useful for delivering medicinal components that are pharmacologically active, and hard to distribute because of their poor water solubility.[9]

***Advantages***

It reduces dosage frequency and adverse effects. Improvement in patient compliance. Increases bioavailability. Reduces gastric irritation. It is possible to prolong biological half-life. It masks the unpleasant taste and odour of drug.[10,11]

***Disadvantages***

Less reproducibility. Materials and processing costs are higher than the traditional preparation. Due to the high drug concentration loaded in microspheres, there is a possibility of dose dumping, which could be harmful. Process variables may affect the stability of the core particles to be encapsulated includes temperature fluctuations, pH shifts, solvent addition, and evaporation.[11-13]

***Ideal properties***

It can accommodate high drug concentration, making it an effective drug delivery system. In aqueous injection vehicles, particles size and dispersibility are controlled. Synthesized preparations should be formulated to ensure stability and shelf life of product that would support therapeutic efficacy. Controlling the release rate for a predetermined amount of time. Serving as a depot, higher concentrations of the medications can be delivered. The carrier enables the drug molecule to maintain its therapeutic effect for an extended period.[12,14,15]

***Types of microspheres***

Different types of microspheres are categorized as, bioadhesive microspheres, magnetic microspheres, floating microspheres, radioactive microspheres, polymeric microspheres, biodegradable polymeric microspheres, synthetic polymeric microspheres

***Bioadhesive microspheres***

Adhesive is a process by which drug sticks to membrane by using water soluble polymers. The adherence of a drug delivery system to a mucosal membrane such as buccal, ocular, nasal, rectal membrane is referred to as bio adhesion. This type of microsphere has longer residence period at target site.[16]

***Magnetic microspheres***

The targeted delivery mechanism is vital for directing the drug to the specific site of disease. This approach enables a smaller dose of magnetically targeted medicine to replace a larger dose of freely circulating medication. Magnetic microspheres, composed of materials such as chitosan and dextran, are integrated into magnetic carriers that respond to magnetic fields, facilitating precise targeting delivery.[17] Magnetic microspheres come in various forms.

*Therapeutic microspheres*

These are designed to target anticancer agents directly to liver tumors, enabling the eradication of tumor cells while sparing surrounding healthy tissue.

*Diagnostic microspheres*

These are utilized for imaging liver metastases and can also distinguish bowel loops from other abdominal structures. They can achieve this by forming nanoparticles composed supra magnetic iron oxides.[18]

***Floating microspheres***

Floating dosage forms have a bulk density lower than that of gastric fluid, enabling them to float on stomach contents without influencing the gastric emptying rates. As the system floats, it releases the drug slowly at a controlled rate, prolong gastric residence and reducing fluctuations in plasma concentration. This approach also minimizes the risk of stomach irritation and dose dumping, ultimately providing a sustained therapeutic effect.[19]

***Radioactive microspheres***

Radioembolization therapy utilizes microspheres, measuring 10-30 μm, which are too large to pass through the capillary bed, and injected into the arteries it supplies to the tumor, these microspheres accumulate and deliver a concentrated dose of radiation, without sparing surrounding healthy tissue.

The microspheres retain their radioactivity acting locally without releasing radiation. Three types of radioactive microspheres are: Alpha (α) emitters, Beta (β) emitters, Gamma (γ) emitters.[20,21]

***Polymeric microspheres***

Polymeric microspheres are classified as.

*Biodegradable polymeric microspheres*

Natural polymers such as starch is a naturally compound it is biodegradable, biocompatible and bioadhesive in nature.

When biodegradable polymers come in touch with mucous membrane, they prolong the residence period, which results in gel formation because of their remarkable swelling capacity in aqueous conditions. The degree and pace of drug release are controlled by the sustained release pattern and the polymer concentration.

*Synthetic polymeric microspheres*

These microspheres are safe and biocompatible and widely used in clinical applications, in addition to being used as bulking agents, fillers, embolic particles etc. These microspheres tend to migrate away from the injection site is one of primary disadvantage, since it raises the possibility of embolism and consequent organ damage.[22]

***Materials used in preparation of microspheres***

Polymers are used in preparation of microspheres. They are divided into two types. Natural polymers and synthetic polymers.[23,24]

***Natural polymers***

They are of three types (a) Carbohydrates examples are chitosan, starch. (b) Protein examples are albumin, gelatin**.** (c) Chemically altered carbohydrates examples are poly dextran

***Synthetic polymers***

They are classified into two categories (a) non-biodegradable polymer, examples are PMMA, epoxy polymers. (b) Biodegradable polymers examples are poly anhydrides.

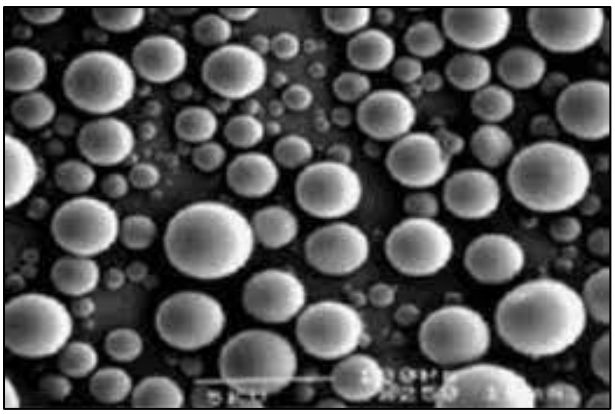

**Figure 1: Microspheres.**

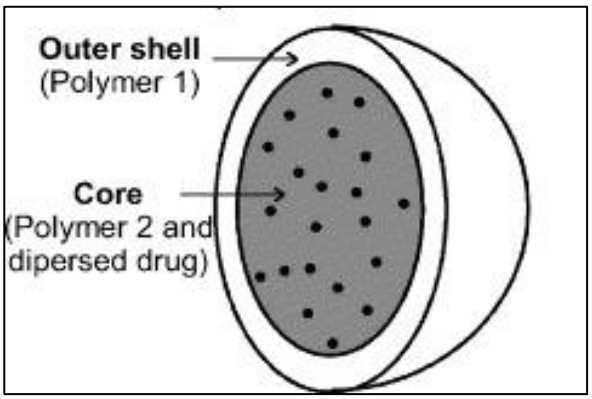


**Figure 2: Cross section of microspheres.**

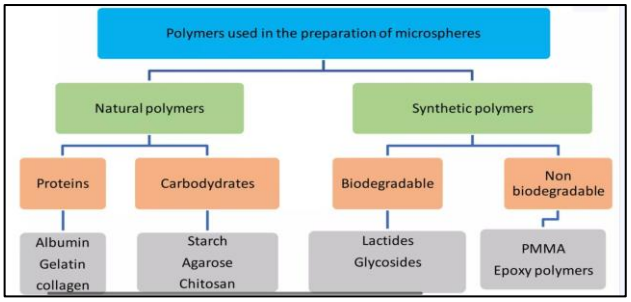


**Figure 3: Classification of polymers used in microsphere preparation.**


**Figure 4: Single emulsion technique.**

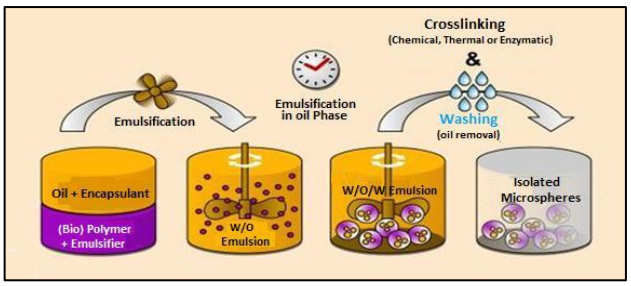


**Figure 5: Double emulsion technique.**

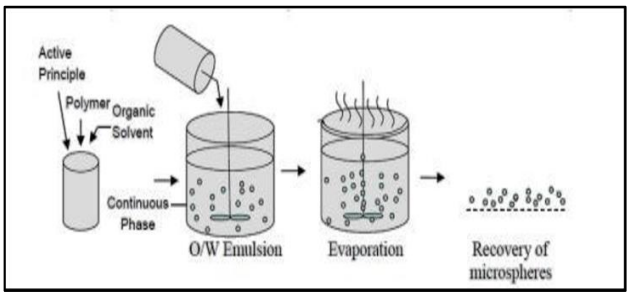


**Figure 6: Solvent evaporation.**

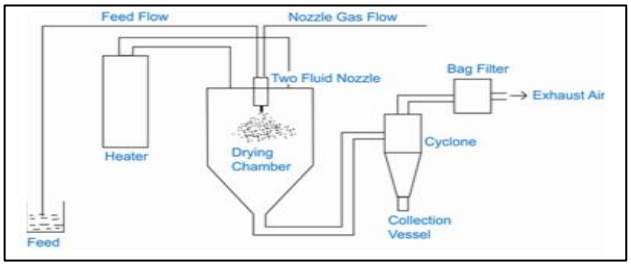


**Figure 7: Spray drying and spray congealing.**

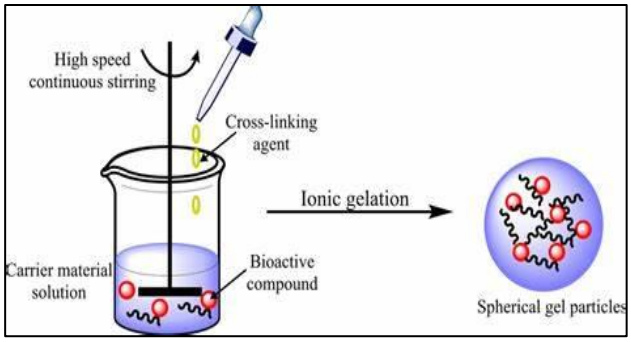


**Figure 8: Ionotropic gelation method.**

***Method used in preparation of microspheres***

There are several ways to prepare microspheres. Single emulsion technique, Double emulsion technique, Solvent evaporation, Spray drying and spray congealing, Quassi emulsion solvent diffusion, Phase separation coacervation technique, Solvent extraction, Ionotropic gelation.

***Single emulsion technique***

Microparticulate carriers of natural polymers like proteins and carbohydrates is feasible with single emulsion technique. After dissolving in an aqueous medium, the natural polymers proceed to a non-aqueous medium, such as oil. Then undergo heating or chemical cross-linking agents can be used to cross connect dispersed globule in following phase. Cross linking chemicals like formaldehyde and glutaraldehyde. Then followed by centrifugation and preparation is cleaned and separated.[25]

***Double emulsion technique***

It is best technique for water-soluble drugs such as proteins, peptides and vaccines. Because it produces several emulsions or double emulsions of w/o/w type. Both synthetic and natural polymers are used in this process. The drug is distributed in aqueous solution and exists in organic phase.[26]

After the drug is dissolved in aqueous phase and encapsulated in organic phase, a primary emulsion is formed, which contains a coated polymer. A secondary emulsion is made by adding aqueous PVA solution after it has been homogenized. Then microspheres are produced, dried and filtered.[2]

***Solvent evaporation***

The solvent evaporation process occurs during production phase. In initial step, the microcapsule coating is dispersed in a volatile solvent that is incompatible with liquid phase of manufacturing vehicle. After the core material is dissolved or dispersed by coated polymer solution, it is microencapsulated.[28]

To create the right size of microcapsule, agitation is necessary to dissolve core material in liquid manufacturing vehicle phase. When they require more heating to cause mixture to evaporate. The core material is dissolved in polymer solution to form matrix-type microcapsules.[29]

***Spray drying and spray congealing***

During this process, the drug and polymer mist are dried in atmosphere. The two processes are known as spray drying and spray congealing are based on cooling the solution or by removing the solvent. Spray drying involves dissolving the polymer in a volatile organic solvent such as dichloromethane or acetone.[30]

Next, polymeric solution is used to rapidly homogenize and distribute the medication. The solvent rapidly evaporates to generate microspheres, which range in size from 1-100 m. Then undergo dispersion and atomized in hot air stream and produces minute droplets. The microparticles are separated from hot air using a cyclone separator and leftover liquid is vacuum and dried.[31]

***Quassi emulsion solvent diffusion***

Acrylic polymer based controlled release medication microspheres were created by quassi emulsion solvent diffusion process.

This method makes micro sponge using an external phase and it contains distilled water, poly vinyl alcohol and the internal phase is composed of drug, polymers and ethanol undergo heating at 60℃. Initially it makes an external phase is left at ambient temperature and continuously stirred for two hours and the mixture is filtered to extract the micro sponge particles.[32]

***Phase separation coacervation technique***

This technique is also known as simple coacervation method involves separating a macromolecular solution into two immiscible liquid phases: A dense coacervate phase and diluted equilibrium phase. Only one macromolecular is present and relatively concentrated.

The presence of two or more macromolecules with opposing charges is referred to as coacervation. It caused by various factors such as temperature, non- solvent addition and interaction between polymers. These can be altered to create microspheres with particular characteristics.[33]

***Solvent extraction***

In order to prepare microparticles the solvent evaporation extracts the organic solvent which removes the organic phase, water miscible organic solvents include isopropyl-alcohol used in this process. The organic phase is extracted using water and it shortens the hardening period of microspheres.[3]

***Ionotropic gelation***

The ionotropic gelation is the capacity of polyelectrolytes to cross-connect in the presence of counter ions to form hydrogel beads, also known as gel spheres. The following formulations can release gel spheres: spherical, cross linked polymeric hydrophilic entities that can significantly gel and swell synthetic biological fluids.[35]

And polymer relaxation regulates the drug release through it, and drug loaded polymer solution is dropped into an aqueous solution of polyvalent cations to create the hydrogel beads.

A three-dimensional lattice of ionically crosslinked moiety is formed when the cation diffuses into the drug loaded polymeric droplets. In order to prevent the three-dimensional structure, biomolecules can load into these gelispheres.[36]

***Natural polymers***

*Alginates*

Formulations of alginates, which are naturally occurring substances presence of both algae and brown sea weed have an attention in pharmaceutical dosage forms. Alginates are used as block polymers including the concentration of alginate and glucuronic acid (MG)blocks, mannuronic acid (M), glucuronic acid(G).[37] When divalent cations like calcium present in the glucuronic acid it blocks and create calcium connected junctions.

Numerous biologically active substances such as proteins, enzymes, DNA, the gelation process can be used to create microspheres which are smaller than 100 m by distributing an alginate solution containing an insoluble calcium salt into oil.

Gelation is accomplished by gently acidifying an oil-soluble acid, which releases calcium ions. It has enhanced surface area and predictable gastro intestinal transit time.[38]

*Gellan*

An anionic deacetylated exocellular polymer, Gellan is secreted by pseudomonas elodea and contains a tetra saccharide repeating unit consists of two β-D-glucose, one β-l-rhamnose and one β-D-glucuronic acid.

Its characteristic is cation-induced gelation which involves creation of double helical junction zones and create three-dimensional network through hydrogen bonding with water and cations.[39]

*Pectin*

An anionic polymer found in cell wall pectin is mostly derived from apple or citrus fruits, A series of D-galacturonic acid-rhamnose make up the majority of structure, Because of its biodegradability and biocompatibility, this polymer find extensive usage in pharmaceutical industry as a gelling or thickening agent.[40]

*Chitosan*

The partial deacetylation of chitin gives chitosan it is a natural cationic biopolymer, the linear β-(1-4) glycosidic connections of 2-acetamido-d-glucose and d-glucose units comprise the biopolymer.

Chitosan based products uses artificial procedure like gelation. It used in waste water treatment, pharmaceutical sector.[41]

*Carboxy methyl cellulose*

Cellulose is the source of carboxy methyl cellulose (CMC), an anionic water-soluble derivative. The repeating units have β-1,4-glycosidic linkages between them.[42] CMC can be cross –linked with ferric or aluminium salt to create biodegradable hydrogel beads and its carboxylic groups can interact with multivalent metal ions to create ionotropic gels.[43]

**Table 1: Different types of microspheres and its applications.**

| Types of Microspheres | Applications [23] |
|---|---|
| **Bio adhesive microspheres** | Distribution of drug through buccal, oral, ocular, nasal, and GI routes; Insulin, GI (glipizide) and nasal (gentamicin) |
| **Magnetic microspheres** | Utilized in protein purification, cell separation, DNA analysis and drug delivery to cancer sites (Doxorubicin) |
| **Floating microspheres** | Drug carriers such as non-steroidal anti-inflammatory medications, anti-viral and antibiotic medicines. Lansoprazole with Prednisolone |
| **Radioactive microspheres** | For medicinal purpose 90Y microspheres for radioembolization of liver and spleen tumors; 212pb-sulfur colloid for local radiation treatment. |
| **Polymeric microspheres** | Delivery of vaccines: Diphtheria toxoid, Hepatitis, influenza, and pertussis, oral administration of medication that break down easily: DNA based plasmid gene therapy. Administration of insulin and LHRH |

**Table 2: List of drugs formulated as microspheres.**

| S. no | Drug | Category | polymer | Method |
|---|---|---|---|---|
| **1** | Fluorouracil | Anti-cancer | Glutaraldehyde | Dry in oil |
| **2** | Gentamycin | Antibiotic | PLGA | Double emulsion |
| **3** | Diclofenac | Anti-inflammatory | Sodium alginate | Gelation method |
| **4** | Insulin | Antidiabetic | Chitosan | Cross linking |
| **5** | Furosemide | Diuretics | Chitosan | Cross linking |
| **6** | Ibuprofen | Analgesic | Sodium alginate | Gelation method |
| **7** | Glipizide | Oral Hypoglycemic | Chitosan | Cross linking |
| **8** | Salbutamol sulphate | Bronchodilator | HPMC | Solvent evaporation |
| **9** | Montelukast sodium | Antiallergic | Carbopol | Emulsion-solvent evaporation |

**Table 3: List of marketed formulation of microspheres.**

| Marketed name | Company name | Disease | Drug |
|---|---|---|---|
| **Nutropin® depot** | Genentech | Growth hormone deficiency | Somatropin |
| **Risperdal®** | Alkermes | Schizophrenia | Risperidone |
| **Lupron Depot®** | TAP | Endometriosis | Leuprolide |
| **Trelstar™ depot** | Pfizer | Prostate cancer | Triptorelin |
| **Suprecur® MP** | Sanofi-Aventis | Prostate cancer | Buserelin |
| **Arestin®** | OraPharma | Periodontitis | Minocycline |
| **Parlodel LAR ™** | Novartis | Parkinson disease | Bromocriptine |
| **Sandostatin LAR®** | Novartis | Carcinoid tumor | Octreotide |

## CHARACTERIZATION OF MICROSPHERES

### *Particle size and shape*

The main methods for imaging microspheres are scanning electron microscopy (SEM) and conventional light microscopy (LM). These are used to assess the microspheres' exterior structure and shape. For double walled microspheres, traditional LM provides control over coating parameters traditional LM provides control over coating. The structure of the microsphere visible before and after coating, and the difference can be measured at the microscopic level. SEM has higher resolution than LM. SEM examines the surface of microsphere as well as the doubled-walled structure formed by particle cross-section. Confocal fluorescence microscopy is a technique used to study the structure of microsphere having many walls. In addition to experimental approaches, laser light scattering and multi-size coulter counters can be used to characterize the microspheres' size, shape, and morphology.[48,49]

### *Angle of contact*

The angle of contact determines microparticles channel moistening potential. Microsphere capacity is evaluated using hydrophobicity and hydrophilicity. To assess the point of contact, the strong air-water interaction is essential. By fastening a bead to a circular cell that is placed over the goal of an enhanced magnifying device, it is possible to determine the moving and retreating point of contact. The contact point transitional temperature of 20°C inside a microsphere.[50]

### *Electron spectroscopy for chemical analysis*

Electron spectroscopy for chemical analysis (ESCA) is used to determine the surface chemistry of microsphere. It can also be used to identify the atomic structure of surfaces. The surface degeneration of biodegradable microspheres can be observed with ESCA spectra.[51]

### *Density determination*

The density of microsphere can be evaluated using a multi volume pycnometer. A cup containing a precisely weighed sample of microspheres is subsequently put inside a multi volume pycnometer. The chamber is filled with helium gas, which is than permitted to expand while the pressure remains constant. As the helium gas expand, the pressure inside the chamber drops, and two consecutive readings of the pressure drop at various initial pressure are noted. These two pressure measurements are used to calculate the volume and density of the sample microspheres.[52]

### *Entrapment efficiency*

Allowing cleaned microspheres to lyse quantifies the microspheres' capture efficiency or entrapment percentage. After that, the lysate is examined to determine its active components in compliance with the monograph's guidelines. Calculating the % encapsulation efficiency may be done using the following formula.[51]

% entrapment= actual content÷theoretical content×100

***Fourier transform-infrared spectroscopy***

When FT-IR is used, the transporter framework's polymeric lattice is deformed. Using rotated complete reflectance (ATR), the examined microsphere surface is estimated. To provide IR spectra, the ATR call goes through the IR bar, which consist mainly of surface material and is often reflected by the example. The ATR-FTIR offers information on the surface organization of microspheres using the unit technique and surrounding variables.[53]

***Percentage yield***

The percentage yield is obtained by dividing the entire weight of the drug and polymer required to make each batch by the weight of the microspheres produced. The results are multiplied by 100.[14]

% yield= practical yield÷theoretical yield×100

***Swelling index***

Microspheres expand in a certain solvent is measured to determine the swelling index. By letting 5 mg of dried microspheres expand overnight in a measuring cylinder with 5 ml of buffer solution, the equilibrium swelling degree may be ascertained. The formula can be used to calculate swelling index.

Swelling index=Wf-Wo÷Wo×10

## PHARMACEUTICAL APPLICATIONS

***Oral drug delivery***

The drug can be administered more easily and conveniently by the oral route and it has greater patient compliance rate. Oral route of administration widely used for variety of medicinal compounds. Mainly oral route improves drug solubility and drug permeability, drug delivery by microspheres shows prolonged release of medication improves patient compliance.[56]

***Ocular drug delivery***

Microspheres make an excellent vehicle for delivering drugs to eyes. When compared to aqueous ocular preparation, the drug bioavailability is increased while using microspheres as drug administration. Microspheres utilized for long lasting release of drugs because of their sustained release mechanism and it lowers dosage frequency.[57]

***Microspheres in cancer treatment***

Liver tumors are treated with ytrium-90 or other radioactive microspheres it contains radioactive emitters. Radioactive microspheres in a suspension with a diameter range of 30 micron are injected into the hepatic artery and enter the tumor vasculature undergo radiation exposure to kill out the tumor cells without endangering healthy cells.5-flurouracil used to treat colon cancer.[58]

***Microspheres in gene delivery***

They are few examples of gene delivery uses microspheres are viral vectors, non-ionic liposomes and microcapsule technology for genotype drug delivery method. While viral vectors are highly effective and have a broad range of cell targeting and crucial for genotype delivery, and they cause harmful effects by activating the immune system.

Non-viral gene therapy delivery techniques have developed to address the viral vectors and it have some benefits like DNA is transported by polymers in gene delivery applications, reduces cell targeting, unrestricted plasmid size.[59,60]

***Monoclonal antibodies***

Microspheres are biologically immunospheres that are targeted by monoclonal antibodies and it can be used to target areas with microspheres it contains bioactive chemicals. There are several ways to attach monoclonal antibodies to microspheres. Non-specific adsorption, specific adsorption, direct coupling, coupling via agent.[61]

***Other applications***

Microspheres are employed in membrane technology it mainly created for fluorescence-connected immune sorbent assay, mass spectrometry and cell biology. Yttrium is a common treatment for hepatocellular cancer and have several uses in microencapsulation in industries, photosensitive paper.[62]

## CONCLUSION

The present review article suggests that microspheres are better drug delivery system and can resolve problems associated with conventional dosage forms. Microspheres are versatile and used in various applications like diagnostics to drug delivery and medical applications. Microspheres formulation shows more potency and having more effectiveness in the drug delivery system and also, they found to be effective carriers for the novel drug delivery system.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Anusha R, Gayathri K, Sindhu T, Shahi RR, Hassan R, Afroz S, Vaishnavi J. Formulation and characterization studies of microspheres. Int J Basic Clin Pharmacol 2025;14:307-15.