

A Comprehensive Review on Microbeads as a Targeted Drug Delivery system

B.Medha Gayathri¹, A.V.Vasanthi², G.Sri Lalitha^{3*}

¹Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya
Hyderabad, Telangana, India.

²Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya
Hyderabad, Telangana, India.

³Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya
Hyderabad, Telangana, India.

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ABSTRACT:

The development of an effective and safe new drug delivery systems has become very important in formulating of various dosage forms. So researchers has focused on new way to delivery drugs for long period of time or for controlled release or sustained release effect to minimize the loss of drug and also to reduce side effect. in the preparation of microbeads mostly natural polymer like sodium alginate used as the matrix because off its natural, biodegradability, low cost, biocompatibility. Sodium Alginate is a non-toxic when taken orally and also shows the protective effect on the mucous membrane of GIT. The gelation of anionic polysaccharide sodium alginate, the primary polymer of natural origin, was achieved with oppositively charged calcium ions and to form microbeads. These are prepared by ion-gelation method, cross-linking, emulsion-gelation method, spray drying, and simple and complex co-acevation phase separation method. This review focused on different types of polymers used, different methods of preparation, and evaluation parameters of sodium alginate microbeads, therapeutic application and their role in controlled or novel drug delivery systems.

Key Words: Different polymers, Ion-gelation method, Cross-linking, Applications.

I. INTRODUCTION:

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired concentration. That is, a drug delivery system should deliver the drug at a rate dictated by the needs of the body over a specific period of treatment. (1) The oral route of drug administration constitutes the most convenient and preferred means of drug delivery into the systemic circulation. This is due to the ease of administration, the higher patient acceptance, adherence and compliance to medication, and the cost-effective manufacturing process. Tablets and capsules are the

most common oral dosage forms and are mostly prepared for immediate release, which enables rapid absorption. Nonetheless, drugs with a low healing index are vulnerable to eliciting detrimental results due to fluctuating drug levels. In addition, drugs with a brief half-existence ought to be regularly administered, which impacts affected person adherence and usual compliance to the remedy regimen. The production of polymeric gel beads is a novel approach for achieving the controlled release of many therapeutic agents. (2)

Microbeads, as the name suggests they are nearly spherical, small with diameter of 0.5-1000 um in size, solid and free flowing particulate carriers containing dispersed drug particles either in solution or a crystalline shape that permit a sustained launch or more than one launch profiles of remedy with numerous energetic dealers without pre dominant facet effects. Additionally, the beads maintain functionality under physiological conditions, can incorporate drugs to deliver locally at high concentration ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low. The microbeads are comprised of numerous polymers including cationic polymers e.g. chitosan, anionic polymers e.g. sodium alginate, and binding components e.g. gelatin, chondroitin sulfate, avidin in predetermined ratio. The use of small and round microbeads of the same size nullifies the disadvantages that are encountered with powders and granules. (1)



Figure 1 Image of Micro beads

ADVANTAGES OF MICROBEADS:

- Control of drug therapy is achieved.
- Rate and amount of drug absorbed can be modified.
- Frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made convenient.
- The safety margin of high potency drugs can be increased. (3)
- Limiting fluctuation within therapeutic range.
- Reducing side effects.
- Decreasing dosing frequency
- Encapsulating drugs within microbeads can enhance their bioavailability. This is particularly useful for drugs with poor solubility or stability
- Microbeads can be designed to target specific sites within the body.
- Microbeads can be used to mask the unpleasant taste or odor of certain drugs
- Enhanced Stability
- Microbeads allow for the incorporation of multiple drugs into a single formulation, enabling combination therapy for the treatment of complex diseases or conditions.

DISADVANTAGES OF MICROBEADS:

- Highly molecular weight compounds have a limited and restricted loading and their release may be difficult.
- Formation of complexes with the blood components.
- There is a high cost of production.
- There is reduced ability to adjust the dose.
- It is a highly sophisticated technology and requires skills to manufacture.
- It is difficult to maintain the stability of dosage form. (3)
- One of the major drawbacks of microbeads is their potential environmental impact. Microbeads are often made of synthetic polymers that do not readily degrade in the environment.
- In response to growing environmental concerns, many countries have started implementing regulations to restrict or ban the use of microbeads in personal care products, including pharmaceuticals
- Achieving uniformity and precise control over the size distribution of microbeads can be challenging during the manufacturing process.
- Microbeads, especially those used in topical formulations, can provide a surface for microbial growth if not properly preserved. This could lead to contamination issues.

MECHANISM OF SUSTAINED RELEASE MICROBEADS:

There are three main mechanisms involved in the release of drugs from microbeads.

It is based upon the type of microbeads formulated. The drug gets either diffused from the membrane or gets enzymatic lysis or hydrolysis when exposed to the surrounding gastric fluids. (3). The sustained release of drugs or other bioactive molecules from microbeads involves complex mechanisms that are influenced by the properties of the microbeads themselves as well as the characteristics of the encapsulated molecules. Here's a general overview of the mechanisms involved in sustained release from microbeads:

1. Diffusion: One of the primary mechanisms of sustained release is diffusion. This occurs when the encapsulated molecules, such as drugs, diffuse through the matrix of the microbeads, gradually releasing into the surrounding environment. The rate of diffusion depends on factors such as the size and structure of the microbeads, as well as the molecular weight and solubility of the encapsulated molecules. Smaller molecules and those with higher solubility typically diffuse more readily.

2. Degradation: Biodegradable microbeads degrade over time, releasing the encapsulated molecules as degradation products. This mechanism is particularly relevant for microbeads made from polymers that undergo hydrolysis or enzymatic degradation in biological environments. As the polymer matrix degrades, it gradually exposes the encapsulated molecules, leading to sustained release over an extended period.

3. Swelling: Microbeads made of hydrogels or other swellable materials can absorb water from the surrounding environment, causing the microbeads to expand. This swelling can create pores or channels in the microbeads, facilitating the diffusion of encapsulated molecules from the matrix. The release rate can be controlled by adjusting the degree of cross-linking or the composition of the hydrogel.

4. Erosion: In addition to degradation, erosion of the microbead matrix can occur due to physical or chemical processes. Mechanical forces, such as shear stress or agitation, can cause surface erosion, where the outer layers of the microbeads gradually wear away, releasing encapsulated molecules. Chemical erosion may also occur through processes such as dissolution or hydrolysis, depending on the composition of the microbeads.

5. Matrix Properties: The properties of the microbead matrix, such as porosity, pore size distribution, and surface area, play crucial roles in determining the rate and mechanism of sustained release. A higher porosity or larger surface area can enhance diffusion and degradation processes, leading to faster release kinetics. Conversely, a

denser matrix or smaller pore size may slow down release rates.

6. Controlled Release Systems: Microbeads can be engineered with specialized coatings, membranes, or multilayer structures to further control the release of encapsulated molecules. For example, coatings may

act as barriers to diffusion, allowing for sustained release over a prolonged period. Alternatively, stimuli-responsive coatings can trigger release in response to specific environmental cues such as pH, temperature, or enzymatic activity.

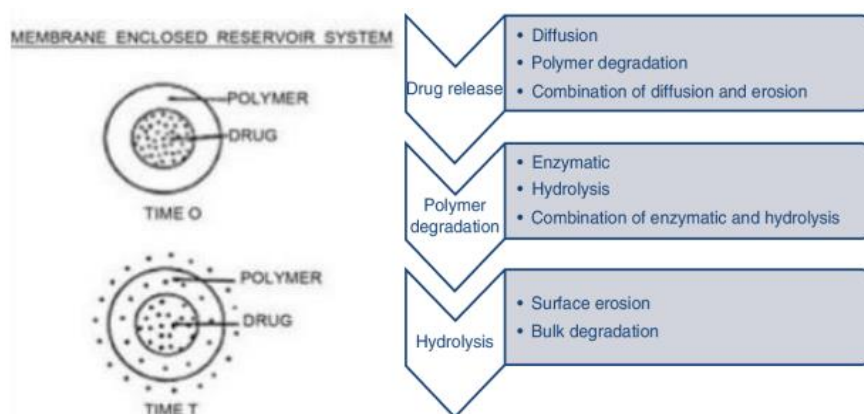


Figure 2 Mechanism of release of Microbeads.

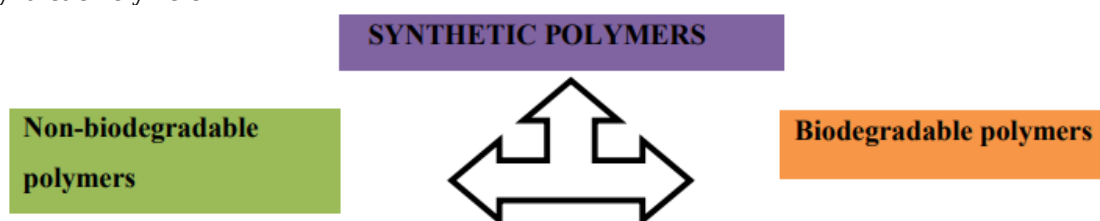
Overall, the sustained release of molecules from microbeads is a complex process influenced by multiple factors, including diffusion, degradation, swelling, erosion, and the properties of the microbead matrix. By understanding and manipulating these mechanisms, researchers can design microbead-based drug delivery systems with tailored release profiles for various therapeutic applications.

1. Synthetic Polymers

POLYMERS USED IN FORMULATION OF MICROBEADS

In the formulation of FDDS, several polymers are used. They are classified into two types:

1. Synthetic Polymers
2. Natural Polymers



Non-biodegradable polymers: – Polymethyl Methacrylate, Glycidyl Methacrylate, Acrylates. Biodegradable polymers: – Lactides and Glycolides, Copolymers, Poly Alkyl Cyano Poly Anhydrides.

2. Natural polymers

In recent years, polymers derived from plant origin have evoked tremendous interest because of their diverse pharmaceutical applications. These herbal gums and Mucilage's are favored over the artificial ones due to the fact they're biocompatible, cheap, and easily available than the synthetic ones.

A. Okra Mucilage

The okra gum is obtained from the natural fresh fruits of the plant *Abelmoschus esculentus* (family: malvaceae). The okra polysaccharide contains the major polysaccharide component differing widely in

the molar ratios of galactose, galacturonic acid, and rhamnose and with some fractions of glucose, mannose, arabinose, and xylose. Mucilage from the pods of *Abelmoschus esculentus* is evaluated for its immunity and suitability as suspending agent. (8)

B. Hibiscus rosa sinensis

Mucilage is obtained from the natural fresh leaves of *Hibiscus rosa-sinensis* (family: malvaceae). Mucilage of *Hibiscus rosa-sinensis* consists of L-rhamnose, D-galactose, D-galacturonic acid, and D-glucuronic acid. The use of its mucilage for the development of sustained launch tablet has been reported. (9,10,11)

C. Tamarind Seed Polysaccharide

Tamarind xyloglucan is obtained from the endosperm of the seed of the tamarind tree, *Tamarindus indica* (family: Fabaceae). Tamarind

gum is a polysaccharide composed of glucosyl: xylosyl: galactosyl within the ratio of 3: 2: 1. It was seen that the matrix tablets prepared by using tamarind gum were able to carry most of the drug to the colon and restrict the release in upper GIT. (12)

D. Fenugreek Mucilage

This mucilage is obtained from seeds of *Trigonella foenum-graceum* (family: Leguminosae). Its seeds contain a high percentage of mucilage and do not dissolve in water but form viscous tacky mass and swell up when exposed to fluid (13)

S. No	Dosage Form	Drugs
1.	Reservoir System tablet	Morphine sulfate
2.	Matrix system tablet	Isosorbite mononitrate, Metformin HCl, Clarithromycin
3.	Diffusion controlled release	Bupropion
4.	Push pull osmotic system	Doxazosin, Verapamil, Glipizide
5.	Ion-Exchange System	Hydrocodon, Dextromethorphan
6.	P ^H dependent system	Aceclofenac, Diclofenac sodium
7.	Altered density formulation	Levodopa and benserazide. ^[5]

Table 2 List of Drugs Formulated with controlled drug delivery

CRITERIA FOR FORMULATION OF MICROBEADS:

A number of formulation methods have been developed to overcome the barrier seen with immediate release oral dosage forms. These processes include inert insoluble matrices, use of coatings, hydrophilic matrices, as well as the combinations of hydrophilic and hydrophobic polymers, embedding of the drug in plastic matrix, ion exchange resins, osmotic pumps and microencapsulation. The physiology of the gastrointestinal tract, the physicochemical property of the drug, the drug release pattern, the pharmacological action of the drug are the parameters that must be considered too.

The physicochemical properties of the drug involve parameters like

- aqueous solubility,
- Stability,
- pKa, and
- permeability values.

Ideal Characteristics of Microbeads are listed as:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation with a clinically acceptable shelf life.
- Controlled particle size and dissolvable in aqueous vehicles for injection.
- Release of the active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability

PROPERTIES OF MICROBEADS:

Here are some key properties of microbeads:

- **Size:** Microbeads are characterized by their diameter, which can vary depending on the application. They can range from a few micrometers to several hundred micrometers in size. Size is a crucial parameter as it influences properties such as surface area, porosity, and interaction with biological systems.
- **Shape:** While microbeads are typically spherical, they can also be engineered into other shapes such as ellipsoids or cylinders. The shape can impact properties like packing density, flow behavior, and interaction with cells or tissues.
- **Material Composition:** Microbeads can be made from a wide range of materials including polymers, metals, ceramics, and hydrogels. The choice of material depends on factors such as biocompatibility, mechanical properties, degradation kinetics, and the intended application of the microbeads.
- **Surface Properties:**
- **Surface Chemistry:** Microbead surfaces can be modified with functional groups, coatings, or biomolecules to impart specific properties such as bioactivity, hydrophilicity, or targeting capabilities.
- **Surface Roughness:** Surface roughness affects properties like cell adhesion, protein adsorption, and drug loading capacity. It can be controlled during microbead fabrication processes.
- **Porosity:** Microbeads can be engineered to be porous, allowing for the encapsulation of drugs, cells, or other bioactive molecules within their structure. Porosity influences properties such as drug loading capacity, release kinetics, and diffusion rates.

- **Mechanical Properties:** The mechanical strength and elasticity of microbeads are important for their stability, handling, and performance in various applications such as tissue engineering, drug delivery, and surgical interventions.
- **Biodegradability:** Biodegradable microbeads are designed to degrade over time in biological environments, facilitating the controlled release of encapsulated drugs or cells and minimizing long-term foreign body responses. The rate of degradation can be tailored by selecting appropriate materials and fabrication methods.
- **Surface Charge:** Microbeads may possess a net positive, negative, or neutral surface charge, depending on their composition and surface modifications. Surface charge influences interactions with biological molecules, cells, and tissues, affecting properties like cellular uptake, protein adsorption, and immunogenicity.
- **Density:** Microbead density affects properties such as sedimentation rate, flow behavior, and

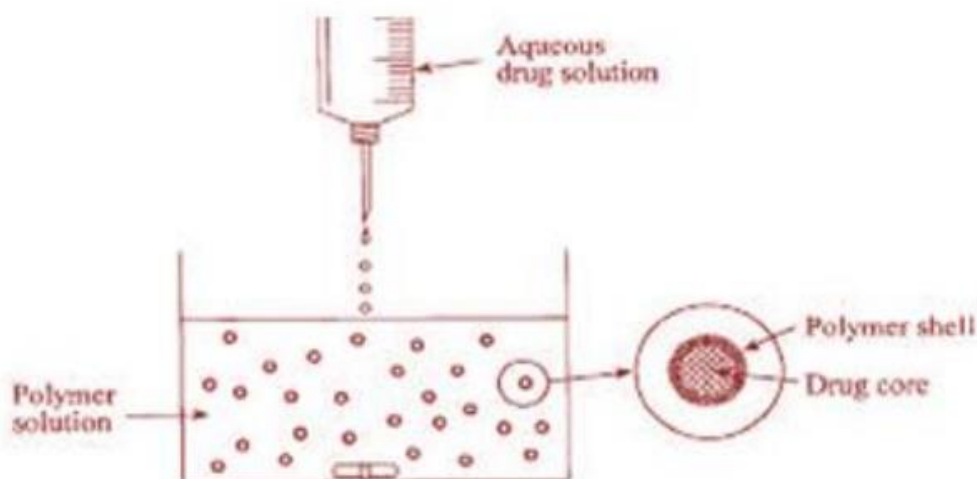
stability in suspension. Density can be adjusted by selecting materials with specific densities or by incorporating additives during fabrication.

- **Optical Properties:** Microbeads can exhibit optical properties such as fluorescence, luminescence, or opacity, depending on their composition and functionalization. These properties are useful for applications such as imaging, diagnostics, and labelling.

TECHNIQUES OF MANUFACTURE OF MICROBEADS:

1. Ionotropic Gelation Method-

It involves the binding that occurs when an ionic polymer interacts with ions that have opposite charges. The concept of electroneutrality cannot adequately describe the interaction between polyanions and cations, in contrast to simple monomer ions. The ability of cations to conjugate with anionic functions, or vice versa, is influenced by their three-dimensional form and the presence of distinct units. The two types of ionotropic gelation methods are as follows:



a. External Gelation Method-

A metal ion solution is used as a source of crosslinking ions in the external gelation process. With delicate movements, the drug-containing polymer solution is pressed into this solution via the needle. The polymer droplet gels instantly upon contact with the metal ion solution, resulting in the creation of self-charming beads. After the beads have set in the gelling medium for a while, they are taken out and allowed to dry. Rapid diffusion of crosslinking ions into partially gelled beads causes external gelation (1)

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Internal Gelation Method:

The cross-linker ion is produced "in situ" when using the internal gelation technique. This method uses an insoluble metal salt as a source of crosslinking cation, such as calcium carbonate or barium carbonate. With the help of pH reduction, the cation is liberated in situ, solubilizing the metallic salt and freeing the metallic ion. (1)

2.Emulsion Gelation Method

Emulsion gelation procedures provide an additional approach to the creation of microbeads. The weighed amount of sodium alginate was dissolved in deionized water to create the sodium alginate solution. To create a homogenous drug-polymeric mixture, a precisely weighed quantity of drug was added to a sodium alginate polymeric solution and the mixture was magnetically agitated with a light temperature. A certain amount of cross-linking agent was added to create a viscous dispersion, which was then injected into oil containing span 80 and 0.2% glacial acetic acid using a syringe fitted with a flat-tipped needle of size no. 23 while being stirred magnetically at 1500 rpm. For thirty minutes, the

microbeads are kept inside the oil to produce rigid, distinct particles. The microbeads were dried at 400° C for 12 hours after being collected by decantation. The items were then separated and cleaned with chloroform to remove any remaining oil strains. (1)

3.Polyelectrolyte Complexation Method: Another method of microbeads preparation is the complex coacervation of oppositely charged polyelectrolytes, polycation and polyanion materials, alginate–chitosan microcapsules with biocompatibility and biodegradability may be prepared under mild conditions, even physiological conditions, so they may be appropriate for the utility in biomedical fields. In current years, there was growing interest within the study of the usage of alginate–chitosan microcapsules administered for the drug-delivery systems of proteins and polypeptides. With this method, specific conditions of polyion concentration, pH and ionic strength, the mixture will separate into a dense coacertive phase containing the microbeads and a dilute equilibrium phase. For example, complex coacervation between alginic acid and chitosan was accomplished by spraying the sodium alginate solution into the chitosan solution, generating strong microbeads that remained steady over a large range of Ph. For the best yield with coacervative bead preparation conditions should be set to a pH of 3.9, an ionic strength of 1 mM, and a 0.15% w/v total polyion concentration. (1)

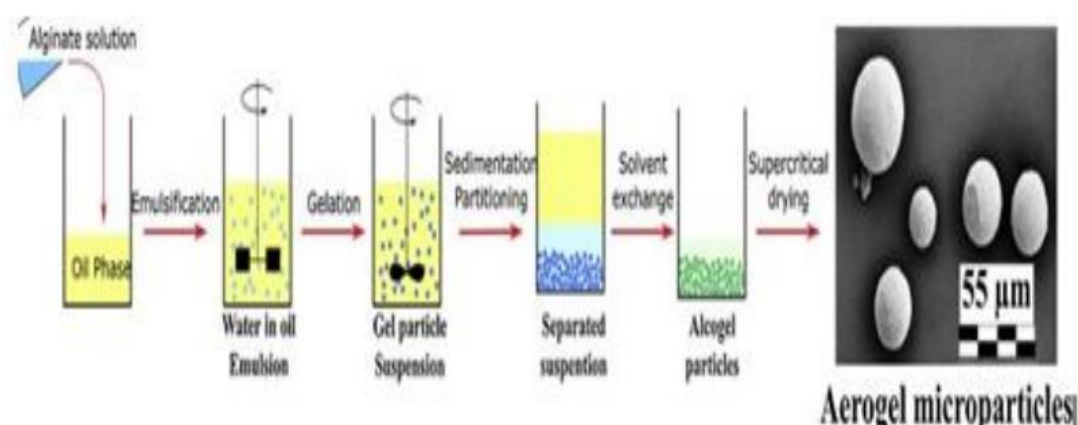


Figure 3 Preparation of Microbeads

APPLICATIONS OF MICROBEADS:

- Microbeads have been found in cleansers/exfoliators, shower/bath products, facial cleansers, creams, deodorants, foundations, nail polishes, eye colors, shaving creams, bubble baths, hair dyes, insect repellents, toothpastes, eye

shadows, blush powders, hair. dyes, liquid make-up, mascara, baby products, emulsions and sunscreens.

- Microbeads can also be observed in different patron uses/merchandise such as cleansing merchandise and printer toner. For example, Napper and Thompson (2015, in press) quantified microbeads incorporated in personal care products

as exfoliants and confirmed that abundance varied considerably among products

- Microbeads also are utilized in business merchandise consisting of abrasive media (e.g., plastic blasting at shipyards, productions centers consisting of garment and vehicle parts), industry (e.g., oil and fuel line, fabric printing, and car molding), different plastics products (e.g., anti-slip and anti-blocking off applications) and clinical applications (biotechnology and biomedical research).

- **Drug Delivery:** Drugs are delivered using microbeads, allowing for regulated and focused release. Improved therapeutic results can result from encasing drugs within microbeads, which offer protection against degradation and regulated release kinetics. To improve site-specific drug delivery, these beads can be made to release medications in response to particular stimuli like pH, temperature, or enzyme activity.

- **Diagnostic Assays:** Diagnostic assays employ microbeads functionalized with certain ligands, such as peptides, antibodies, or nucleic acids, to find biomarkers linked to a range of illnesses. Functionalized microbeads have the ability to attach themselves to target molecules present in biological samples. This property makes detection techniques such as immunoassays, flow cytometry, and nucleic acid hybridization tests more precise and sensitive.

- **Tissue Engineering:** Microbeads are scaffolds or transporters for cells, growth factors, and other bioactive compounds in tissue engineering applications. For the development of cells and the

regeneration of tissue, they offer structural support and spatial structure. Biocompatible microbeads, such as hydrogels or polymers, can be used in regenerative medicine techniques because they imitate the extracellular matrix and encourage cell adhesion, proliferation, and differentiation.

- **Cell Encapsulation:** Microbeads are used to encapsulate cells, particularly in transplantation and cell-based therapy. They permit the interchange of nutrients, oxygen, and waste products with the surrounding environment while shielding encapsulated cells from immunological rejection. Numerous uses of this encapsulation technology have been investigated, including islet cell transplantation for the treatment of diabetes, enzyme replacement therapy, and cell-based cancer therapeutics.

- **Surgical Hemostasis:** During surgery, hemostatic microbeads are used to stop bleeding. Usually composed of biodegradable substances like collagen or gelatin, these microbeads are intended to stick to tissue and form a seal that will fast halt bleeding. They are especially helpful in minimally invasive procedures where it could be difficult to reach bleeding spots.

- **In Vivo Imaging:** It is possible to create microbeads to function as contrast agents for magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound, among other imaging modalities. Contrast agents can be added to the microbead structure to improve the visibility of particular tissues or biological processes, which can help with research and diagnostic imaging applications.



Figure 3 Applications of Microbeads

EVALUATION OF MICROBEADS:

The evaluation of microbeads typically involves assessing various characteristics such as their physical properties, biocompatibility, functionality, and performance in specific applications. Here's a breakdown of the key aspects involved in the evaluation process:

Physical Properties:

- **Size Distribution:** Using methods like laser diffraction, dynamic light scattering, or microscopy, the size distribution of microbeads is measured.
- **Shape:** An assessment of the microbeads' form, which might affect characteristics such as flow patterns, density of packing, and interactions with biological systems.
- **Surface Area:** The measurement of a microbead's surface area, which influences its ability to bind to cells, load drugs, and interact with their surroundings.

Chemical Composition:

- **Material Composition:** Determining the polymer or material utilized in the creation of microbeads as well as their chemical makeup.
- **Surface Functionalization:** Determining the nature of any surface alterations or functional groups incorporated into the microbeads for particular uses, including biomolecule targeting or immobilization.

Biocompatibility:

- **Cytotoxicity:** Evaluation of the possible harmful effects of microbeads on cells by the use of in vitro tests, including assays for apoptosis, proliferation, and cell viability.
- **Immunogenicity:** Assessment of the immune reaction that microbeads trigger when they come into contact with biological systems, taking into account the possibility of immunological rejection or inflammation.

Drug Release Kinetics:

- **In vitro Release Studies:** Evaluation of the kinetics of medication or bioactive molecule release from microbeads in physiologically appropriate settings, including rate, duration, and mechanism of release.
- **Release Profile Analysis:** Analyzing the burst, sustained, or controlled release patterns of medications that have been encapsulated.

Stability and Degradation:

- **Degradation Profile:** Tracking the behavior of microbeads as they break down over time, taking into account variables including rate, products, and physical property changes.
- **Studies on Stability:** assessment of the stability of microbeads under different storage circumstances, taking into account variables

including exposure to light, humidity, and temperature.

Performance in Target Applications:

Functional Assays: Evaluation of the effectiveness of microbeads in certain uses, like medication administration, tissue engineering, assays for diagnosis, or surgical procedures.

- **In Vivo Studies:** Analyzing the behavior and effectiveness of microbeads in clinical trials or animal models; includes biocompatibility, pharmacokinetic and pharmacodynamic evaluations, and therapeutic results.

Safety and Regulatory Considerations:

- **Regulatory Compliance:** Ensuring that, in healthcare applications, microbeads adhere to regulatory criteria for safety, efficacy, and quality control.
- Risk assessment is the process of identifying and reducing any possible dangers connected to the use of microbeads, such as toxicity, immunogenicity, and environmental impact issues.



II. CONCLUSION:

In conclusion, microbeads offer a promising option for continuous drug delivery systems in pharmacies, offering several advantages such as controlled release, improved patient compliance and targeted therapy. Their versatility in manufacturing methods allows size, shape and composition to be tailored to specific drug dosage needs. In addition, microbeads provide protection for sensitive drugs, which increases stability and bioavailability. From sustained release to targeted delivery, microbeads offer precise mechanisms to optimize drug efficacy and minimize side effects. Through innovative production methods and rigorous evaluation methods, the pharmaceutical industry can exploit the full potential of microbeads and ensure their safety and durability. However, challenges such as the risk of explosion and environmental concerns associated with non-biodegradable microbeads require careful consideration. Through continuous research and

innovation, addressing these challenges and developing biodegradable alternatives will optimize microbead-based drug delivery systems for safer and more effective drug use. Overall, microbeads hold significant promise for advancing drug delivery technology, improving patient outcomes and solving health challenges in the future.

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