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Microencapsulation – The Drug Delivery System



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ABSTRACT

The microencapsulated carrier technology provides an interesting as well as an effective approach for the delivery of a drug. It offers the delivery of the drug by coupling the drug to a carrier particle such as microsphere. Microspheres can be used to deliver the drug in a rate-controlled manner. Medication is released from a microsphere by the degradation of the polymer matrix or by drug leaching from the polymer. The present review provides a detailed discussion of therapeutic aspects of microsphere drug delivery including the advantages and disadvantages of microspheres, preparation of microspheres, carriers used, characterization, and applications of microspheres. Microspheres are one of the most promising targeted and effective drug deliveries.

INTRODUCTION

Microspheres are widely used constituents of multi-particulate drug delivery systems, offering both therapeutic and technological advantages. A well-designed controlled drug delivery system can overcome the problems of conventional therapy and increases the therapeutic efficacy of the given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the drug to the target tissue in the minimal amount at the right time and causes little toxicity and fewer side effects.¹ There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One of the approaches is using microspheres as carriers for drugs. Microspheres are free flowing solid particles made up of biodegradable and non-biodegradable material, biodegradable synthetic polymers, and modified natural products such as starch, gums, proteins, fats, and waxes. The natural polymers include albumin and gelatine, the synthetic polymer includes polylactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials will be selected according to the drug solubility, stability, process safety, and economic considerations,² which is ideally having a particle size less than 200 μm . They can be delivered through various routes like oral, nasal, rectal, parenteral, ophthalmic, vaginal and transdermal etc.^{3,4} Spray drying and milling can thermally denature some compounds. Polymer phase separation, spray drying, and emulsification processes often lead to an amount of residual solvent that is higher than authorized values. Near critical or supercritical fluid techniques are promising and fulfil some of the new requirements.⁵

Types of microspheres

Bio adhesive microspheres

Adhesion can be defined as the sticking of drugs to the membrane by using the sticking property of the water-soluble polymers. Adhesion of the drug delivery device to the mucosal membrane such as buccal, ocular, nasal, rectal, etc. can be termed as bio adhesion. These types of microspheres show a prolonged residence time at the site of application and cause intimate contact with the absorption site and produce better therapeutic action.⁶

Magnetic microspheres

The magnetic drug transport technique is based on the fact that the drug can be either conjugated on the surface of the microsphere or encapsulated into a magnetic microsphere. When the magnetic carrier is intravenously administered, the accumulation takes place within

the area to which the magnetic field is applied & often augmented by magnetic agglomeration. The accumulation of the carrier at the target site allows magnetic microspheres to deliver the drug locally. The efficiency of accumulation of magnetic carriers on physiological carriers depends on physiological parameters like field strength, particle size, surface characteristic, and blood flow rate, etc. The magnetic field helps to outbreak the magnetic carrier into the targeted area. The very high concentration of chemotherapeutic agents can be attained near the target site without any toxic effect to normal surrounding tissue or the whole body. It is possible to replace a large amount of drug targeted magnetically to the diseased site, reaching effective and up to several-fold increased drug levels. The different types of magnetic microspheres include therapeutic magnetic microspheres and diagnostic microspheres.

a. Therapeutic magnetic microspheres

Therapeutic magnetic microspheres are used to deliver the chemotherapeutic agent to the liver tumour. Drugs like proteins and peptides can also be targeted through this system.

b. Diagnostic microspheres

Diagnostic microspheres can be used for imaging liver metastases and also can be used to differentiate bowel loops from other abdominal structures by forming nano-sized particles of supra magnetic iron oxides.⁷

Floating microspheres

In the floating types, the bulk density is less than the gastric fluid and so remains buoyant in the stomach without affecting the gastric emptying rate. The drug is slowly released at the desired rate if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. And it also reduces the chances of striking and dose dumping. One another way it produces a prolonged therapeutic effect and therefore reduces dosing frequencies.^{8,9}

Radioactive microspheres

Radio immobilization therapy microspheres sized 10-30 nm is larger than capillaries and gets trapped in the first capillary bed when they come across. They are injected into the arteries that lead to the tumour of interest. So, in all these conditions radioactive microspheres deliver a high radiation dose to the targeted areas without damaging the normal surrounding tissues.

It differs from the drug delivery system in such a way that the radioactivity is not released from microspheres but acts within a radioisotope.¹⁰

Polymeric microspheres

The different types of polymeric microspheres can be categorized as follows:

a. Biodegradable polymeric microspheres

Natural polymer like starch is used with the concept that they are biodegradable, bio adhesive, and also biocompatible in nature. Biodegradable polymer prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with an aqueous medium. The main drawback of clinical use is the drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.

b. Synthetic polymeric microspheres

The synthetic polymeric microspheres are most widely used in clinical application, moreover, it is also used as a bulking agent, embolic particle, filler, drug delivery vehicle, etc and proved to be safe and biocompatible.¹¹

Advantages of microspheres¹²

1. Size reduction leads to an increase in surface area which can enhance the solubility of the poorly soluble drug.
2. Provide constant drug concentration in the blood which can increase patient compliance.
3. Decrease dose and toxicity.
4. Coating of drug with polymers helps the drug from enzymatic cleavage hence found to be best for drug delivery.
5. Less dosing frequency leads to better patient compliance.
6. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
7. Protects the GIT from irritant effects of the drug.
8. Convert liquid to solid form and mask the bitter taste.

9. It delivers the drug to the target site with specificity to maintain the desired concentration at the site of interest.
10. Reduce the reactivity of the core with the outside environment.
11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal. Particle size reduction for enhancing solubility of the poorly soluble drug.
12. Microsphere morphology allows a controllable variability in degradation and drug release.
13. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitations of microspheres^{13,14}

Some of the disadvantages were found to be as follows:

1. The costs of the materials and processing of the controlled release preparation are substantially higher than those of standard formulations.
2. The fate of the polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants, and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation, or biological agents.
7. Differences in the release rate from one dose to another.
8. The modified release from the formulations.
9. Dosage forms of this kind should not be crushed or chewed.

Excipients used in the preparation

The formulation is usually based on polysaccharides or proteins, but waxes and lipids also play a role in the construction. Nonpolymeric excipients play a role in crosslinking the polymer chains (CaCl₂, glutaraldehyde, poly-L-lysine, etc.), thus forming and hardening the polymer network of the drug delivery systems. The most commonly used polymers are,¹⁵

- **Proteins and waxes of animal or plant origin used in microencapsulation.**

Gelatine, Casein, Whey protein, Albumin, Zein, Soy protein, Gluten, Bees-wax (Apis mellifera), Carnauba wax (Copernicacerifera), Paraffin (hard) (mineral).

- **Polysaccharides of various origins used in microencapsulation.**

Chitosan (deacylated chitin), Sodium hyaluronate, Starch (wheat, corn, potato, rice, tapioca), Guar gum, Locust bean gum (LBG)/carob, Ceratonia, Konjac gum, K, ι , λ -, Carrageenan, Agarose, Sodium alginate, Tragacanth, Gum arabic/ Acacia gummi (Ph. Eur.), Pectin (low or high methoxylated) (apple, citrus peel, beet).^{16,17}

- **Polysaccharides of microbial fermentation used in microencapsulation.**

Xanthan gum, Gellan gum, Dextran, Pullula.

- **Cellulose derivatives applied in microencapsulation.**

Methylcellulose (MC), Carboxymethylcellulose sodium (CMC-Na), Hydroxypropyl cellulose (HPC), Hydroxypropyl methylcellulose (HPMC), Ethylcellulose, Cellulose acetate butyrate.

- **Synthetic polymers applied in microencapsulation.**

Poly (lactic acid) (PLA), Polylactic acid-glycolic acid copolymer (PLGA), Polyacrylic acid (Carbopol), Polymethacrylates, Poly-(Isopropylacrylamide), Polyethylene glycols, Fumaryl diketopiperazine (FDKP).¹

Preparation of Microspheres

a. Solvent Evaporation and Solvent Extraction:

This method is used for the preparation of microparticles, which involves the removal of the organic phase by extraction of the organic solvent. The method involves a water-miscible organic solvent and the organic phase is removed by extraction with water. The process decreases the hardening time for the microspheres. One of the distinct processes involves the

direct addition of the drug. The solvent removal rate depends on the temperature of the water, the ratio of emulsion volume to the water, and the solubility profile of the polymer.¹⁸

b. Spray Drying and Congealing:

These methods are based on the drying of the mist of the polymer and drug in the air. Based on the cooling of the solution and removal of the solvent, these two processes are named respectively. Atomization lead to the formation of small droplets from which the solvent evaporates leads to the formation of microspheres in a size range of 1-100 μ m. Microspheres are then separated from the hot air using the cyclone separator and the solvent is removed by vacuum drying.¹⁹

c. Single emulsion technique:

Several Carbohydrates and Proteins are mainly prepared by this technique. In this technique, natural polymers are first dissolved in an aqueous medium and then dispersed in a non-aqueous medium (oil phase) followed with next step crosslinking of dispersed globule; which can be achieved by 2 methods:

- By Heat: Addition of dispersion into heated oil, but this method is not suitable for thermolabile drugs.
- By Chemical Cross-linking Agent: Using glutaraldehyde, formaldehyde, acid chloride, etc. as a cross-linking agent. Chemical cross-linking suffers the disadvantage of excessive exposure.

d. Double emulsion technique:

The double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins, and the vaccines. This method can also be used with the natural as well as synthetic polymers. The aqueous protein solution is suspended in the lipophilic organic continuous phase. The active constituents are also present in the protein solution. The continuous phase is generally consisting of the polymer solution that eventually encapsulates the protein, contained in the dispersed aqueous phase. The primary emulsion is exposed then to the homogenization or the sonication before addition to the aqueous solution of the polyvinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent extraction or by solvent evaporation.

Many hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist, proteins/peptides, vaccines, and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/extraction.²⁰

e. Polymerization techniques:

The polymerization method conventionally used for preparing the microspheres are mainly classified as:

- Normal polymerization
- Interfacial polymerization. Both are carried out in the liquid phase.
- **Normal polymerization:**

1) Bulk polymerization:

A monomer or a mixture of monomer along with the initiator is usually heated to initiate the polymerization and carry out the process. The catalyst or the initiator is added to the reaction mixture to facilitate or accelerate the rate of the reaction. The polymer so obtained may be moulded or fragmented as microspheres.

2) The suspension polymerization:

It is carried out by heating the monomer or mixture of monomers with active principles (drugs) as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives.

3) The emulsion polymerization:

However, differs from the suspension polymerization due to the presence of the initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules.

- **Interfacial polymerization:**

In the Interfacial polymerization technique two reacting monomers are employed; one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. The continuous phase is generally aqueous in nature from which the second monomer is emulsified. The monomers present in phase diffuse rapidly and polymerize rapidly at the interface. Two conditions arise depending upon the solubility of the formed polymer in the

emulsion droplet. If the polymer is soluble in the droplet it will lead to the formation of the monolithic type of the carrier on the hand if the polymer is insoluble in the monomer droplet, the formed carrier is of capsular (reservoir) type. The degree of polymerization can be controlled by the reactivity of the monomer chosen, their concentration, and the composition of the vehicle of either phase and by the temperature of the system. Controlling the size of droplets or globules of the dispersed phase can control the particle size. The polymerization reaction can be controlled by maintaining the concentration of the monomers, which can be achieved by the addition of an excess of the continuous phase. The interfacial polymerization is not widely used in the preparation of the microparticles because of certain drawbacks, which are associated with the process such as,

- Toxicity associated with the unreacted monomer
- The high permeability of the film
- High degradation of the drug during the polymerization
- Fragility of microcapsules
- Non-biodegradability of the microparticles.²¹

f. Spray drying technique

In this technique, the polymer is dissolved in a volatile organic solvent like dichloromethane, acetone, etc and then the drug (solid form) is dispersed in a polymer solution under high speed homogenization. The dispersion is then atomized in the hot air stream and thus atomization leads to the formation of small droplets from which the solvent evaporates instantaneously; leading to the formation of a microsphere in a size range of 1-100 μm . Prepared microparticles are separated by hot air by the help of a cyclone separator and solvent traces are removed by vacuum drying.²²

g. Phase separation coacervation technique

The phase separation technique is mainly designed for preparing the reservoir type of the system. This method is used to encapsulate water soluble drugs such as peptides, proteins, and some preparations having matrix type particular when the drug is hydrophobic like steroids. The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer-rich phase called the coacervates. The coacervation can be brought about by the addition of the third component to the system

which results in the formation of the two phases, one rich in polymer, while other not, i.e. supernatant, depleted of the polymer. Various methods are effectively employed for coacervates phase separation. The methods are based on the salt addition, on-solvent addition, addition of the incompatible polymer.²³

Physicochemical Evaluation Characterization

The characterization of the microencapsulated carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug, or antigen delivery. These microspheres have different microstructures. These microstructures help to determine the release and the stability of the carrier.

1. Particle size and shape

Conventional light microscopy (LM) and scanning electron microscopy (SEM) is the most widely used procedures to visualize the microparticles. Both of these methods can be used to determine the shape and outer structure of microparticles. LM gives control over coating parameters in the case of double walled microspheres. The structures of microspheres can be visualized before and after coating and their change can be measured microscopically. SEM allows higher resolution in contrast to the LM¹⁷ and also it allows the investigations of the surfaces of the microspheres 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 structural characterization of multiple walled microspheres. Laser light scattering and multi-size coulter counter other than instrumental methods can be used for the characterization of shape, size, and morphology of the microspheres.

2. Density determination

The density of microspheres can be measured by using a multi-volume pycnometer. Accurately weighed sample in a cup is placed into the multi-volume pycnometer. At constant pressure, helium is introduced in the chamber and allowed to expand. This helium expansion results in a decrease in pressure within the chamber. The two consecutive readings of reduction in the pressure at different initial pressure are noted. From two pressure readings, the volume and hence the density of microsphere carriers is determined.²⁴

3. Electron spectroscopy for chemical analysis:

By using the electron spectroscopy for chemical analysis (ESCA), the surface chemistry of the microspheres and also provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surficial degradation of the biodegradable microspheres.

4. Attenuated total reflectance Fourier Transform Infrared Spectroscopy:

The degradation of the polymeric matrix of the carrier system can be determined by FTIR. By measuring alternated total reflectance (ATR) the surface of the microspheres can be investigated. The IR beam passing through the ATR cell reflected several times through the sample to produce IR spectra mainly of surface material. The ATR-FTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

5. Isoelectric point:

The micro electrophoresis is an apparatus that is used to measure the electrophoretic mobility of microspheres through which the isoelectric point can be determined. The mean velocity at different pH values ranging from 3 to 10 is calculated by measuring the time of particle movement over a distance of 1 millimetres. The electrical mobility of the particle can be determined by using this data and the electrophoretic mobility can be related to surface contained charge, ionizable behaviour, or ion absorption nature of the microspheres.

6. Angle of contact

The angle of repose θ of microspheres, which measures the resistance to particle flow is calculated as where $2h/d$ is the surface area of the free-standing height of microspheres heap that is formed after making microspheres flow from the glass funnel.

7. Surface amino acid residue:

The radioactive c^{14} -acetic acid conjugate is used to determine the surface-associated amino acid residue. The carboxylic acid residue is measured through the liquid scintillation counter and hence the amino acid residue can be determined indirectly. EDAC is used to condense the amino group and the c^{14} acetic acid carboxylic acid residue. The technique used for determining the free amino or the free carboxylic acid residues are based on indirect estimation, by measuring the radioactivity of the c^{14} having acetic acid or the glycine

conjugate. The accuracy of the method, however, depends on the time allowed for conjugation of the radioactive moiety and the reactivity of the free functional group.

8. Modified Keshary Chien Cell:

It is a specialized apparatus designed in the laboratory. It is comprised of a Keshary Chien cell containing distilled water (50ml) at 37°C as a dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.^{25,26}

9. *In vitro* methods

There is a need for experimental methods that permits the release characteristics and permeability of the drug via a membrane to be determined. Due to this purpose, several *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies have been used as a quality control procedure in pharmaceutical production, product development, etc. Reproducible and Sensitive release data derived from physicochemical and hydrodynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating *in vivo* conditions has led to the development of several *in vitro* release methods for buccal formulations; however, there is no standard *in vitro* method yet been developed. The various workers have used the apparatus of varying designs and under varying conditions, depending on the application and shape of the dosage form developed.

10. Beaker method

In this method, the dosage form is made to adhere to the bottom of the beaker containing the medium and stirred uniformly using an overhead stirrer. The volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.²⁷⁻²⁸

11. Interface diffusion system

This method is developed by Dearden and Tomlinson. It consists of four compartments. The compartment A represents the oral cavity, and initially contained a definite concentration of drug in a buffer. Compartment B represents the buccal membrane, contained 1-octanol, and compartment C represents body fluids, containing 0.2 M HCl. The compartment D represents protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a syringe.

12. Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements, paddle²⁹⁻³¹ and basket.^{32,33} Dissolution medium used for the study varied from 100 to 500 ml and the rotation of speed from 50-100 rpm.

13. *In vivo* methods

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrants at the surface. The earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However, the widely used methods include *in vivo* studies using buccal absorption tests, animal models, and perfusion chambers for studying drug permeability.

14. Animal models

Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers, or evaluating a set of formulations. Several different animal models have been stated in the literature, however, very few *in vivo* (animal). Animal models such as the dog, rats, rabbits, cat, hamster, pigs, and sheep have been reported. Commonly the procedure involves anesthetizing the animal followed by administration of the dosage form. In rats, the oesophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn and analyzed.³⁴

15. Buccal absorption test

The buccal absorption test was developed by Beckett and Triggs in 1967. This method is simple and reliable for measuring the extent of drug loss of the human oral cavity for single and multi-component mixtures of drugs. This test has been successfully used to investigate the relative importance of drug structure, initial drug concentration, contact time, and Ph of the solution while the drug is held in the oral cavity.³⁵

APPLICATIONS OF MICROSPHERES:

1. Ophthalmic Drug Delivery
2. Oral drug delivery

3. Gene delivery
4. Nasal drug delivery
5. Intratumorally and local drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery
8. Transdermal drug delivery
9. Colonic drug delivery
10. Vaginal drug delivery
11. Targeting by using microparticulate carriers
12. Chemoembolization

1. Ophthalmic Drug Delivery: Microspheres developed using polymer exhibits favourable biological behaviour such as bioadhesion, permeability-enhancing properties, and interesting physicochemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. e.g. Chitosan, Alginate, Gelatin.

2. Oral drug delivery: The ability of microspheres containing polymer to form films permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. pH sensitivity coupled with the reactivity of the primary amine groups makes the microspheres more suitable for oral drug delivery applications. e.g. Chitosan, Gelatin.

3. Gene delivery: Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. e.g. Chitosan, Gelatin, viral vectors, cationic liposomes, polycation complexes.

4. Nasal drug delivery: Polymer-based drug delivery systems, such as microspheres, liposomes, and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. e.g. Starch, Dextran, Albumin, Chitosan + Gelatin.

5. Intratumoral and local drug delivery: To deliver paclitaxel at the tumour site in therapeutically relevant concentration, polymer films are fabricated. A mixture of the drug

has promising potential for use in controlled delivery in the oral cavity. e.g. Gelatin, PLGA, Chitosan, and PCL.

6. Buccal drug delivery: Polymer is one of the excellent substances used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. e.g. Chitosan, Sodium alginate.

7. Gastrointestinal drug delivery: Polymer granules having internal cavities prepared by deacidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug. e.g. Eudragit, Ethyl cellulose + Carbopol BSA, Gelatine.

8. Transdermal drug delivery: Polymer is having a good film-forming property. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. e.g. Chitosan, Alginate, PLGA.

9. Colonic drug delivery: Polymer has been used for the specific delivery of insulin to the colon. e.g. Chitosan.

10. Vaginal drug delivery: Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract. e.g. Chitosan, Gelatin, PLGA.

11. Targeting by using microparticulate carriers: Pellets are prepared with the polymer by using the extrusion/spheronization technology. e.g. Chitosan, Microcrystalline cellulose.³⁶⁻³⁸

12. Chemoembolization: Chemoembolization is an endovascular therapy, which involves the selective arterial embolization of a tumour together with simultaneous or subsequent local delivery of the chemotherapeutic agent. The theoretical advantage is that such embolization will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour. Chemoembolization is an extension of traditional percutaneous embolization techniques.³⁹

CONCLUSION

The microspheres being a good carrier and the micron size gives targeted and effective drug delivery and produces an effective therapeutic action. Microspheres drug delivery is safe and utilized in various areas like floating, drug targeting, vaccine, and vaginal delivery, etc. Microspheres drug delivery covers a vast area of drug targeting. Preparation, procedure & evaluation for microspheres formulations are widely available with effective reproducibility.

Microspheres drug delivery covers a large area of drug targeting hence required consistence performance study to correlate the *in vivo* performance. In the future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

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