CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Review Article*

MICROSPHERES AS CONTROLLED DRUG DELIVERY SYSTEM: AN UPDATED REVIEW

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Article Received: July 2021 **Accepted:** August 2021 **Published:** September 2021

Abstract:

One of the specialties of microspheres is that they are controlled systems of drug delivery designed for sustained release, to reduce the ordinary dose frequency and easy patient compliance. Controlled drug delivery of microspheres to enhance bioavailability, stability, efficiency, and to reduce the toxicity of drug into the body. The preparation is done for targeted local site delivery with a predetermined rate. Microspheres are a significant part of a novel drug delivery system and have solid spherical particles showing free-flowing properties and the particle size range 1-1000μm. Microspheres are matrix-type systems in which the drug is entrapped, dissolve, suspended. Generally solid or liquid drug entrap, dissolve in a matrix system prepared by several types of microspheres such as Bioadhesive microspheres, Magnetic microspheres, floating microspheres, polymeric microspheres, radioactive microspheres. And the following techniques are used in the preparation of various types of microspheres such as spray drying technique, single emulsion technique, Double emulsion technique, solvent evaporation, phase separation coacervation technique. The review of microspheres follows the introduction, characteristics, Advantages, limitations, types of microspheres, method of preparation, evaluation, and application of microspheres.

Keywords: Bio-adhesive microspheres, controlled drug Delivery, entrap dissolve matrix, enhance the bioavailability, floating microspheres.

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Please cite this article in press Rekha pal and G. Gananarajan, ***Microspheres As Controlled Drug Delivery System: An Updated Review.,*** *Indo Am. J. P. Sci, 2021; 08(9).*

INTRODUCTION:

In 1997, firstly microspheres were developed for sustained action of the dosage form. Since then, Microparticles have been found beneficial for sustained and controlled release of drugs and have generated interest as an alternative to conventional or Immediate-release formulations. The particles are also beneficial to deliver the pharmacologically active but low solubility in water. Microsphere-based Formulations can release a constant amount of drugs in the blood or can perform targeted delivery to a desired site in the Body. [1]

Microspheres are solid spherical particles with sizes in the range from 1-1000 µm. They are spherical free-flowing particles prepared by biodegradable synthetic polymer or proteins. There are two types of microspheres:

a. Microcapsules
b. Micromatrices.

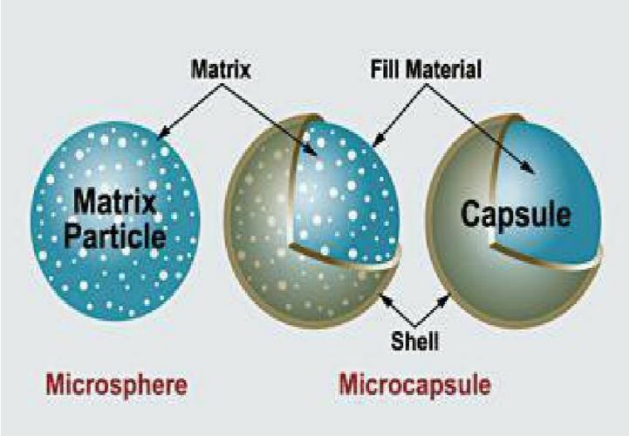

Figure 1:Diagram of microspheres and microcapsule

Microcapsules are those in which entrapped substance is distinctly surrounded by different capsule shells and Micromatrices in which entrapped substance is dispersed throughout the microsphere's matrix. Biodegradable rigid Microspheres incorporating a drug dispersed or dissolved through particle-matrix have the potential for the controlled release of the drug. Microspheres are prepared by polymeric, waxy, or Other protective materials, that is, biodegradable synthetic Polymers and modified natural products.[2]

Table 1:Microsphere properties [3]

Characteristics:

S. No.	Property	Consideration
01	Size	Diameter, Uniformity/ Distribution
02	Composition	Density, RI, Hydrophobicity, Hydrophilicity, Nonspecific binding, Autofluorescence
03	Surface chemistry	Refractive groups, Level of functionalization charge
04	Special properties	Visible dye/fluorophore, Super-paramagnetic

Advantages

1. It gives a constant and prolonged therapeutic effect.
2. It can be injected into the body caused by the spherical shape and smaller size.
3. They can control variability in degradation and drug release.
4. Proper drug utilization improves bioavailability and reduces the incidences of Intensity of adverse effects.
5. It reduces dosing frequency and hence improves patient compliance. [4]
6. This system is Capable of protein, Enzyme delivery.
7. Target drug delivery is possible.
8. It gives constant drug concentration in blood.
9. Easy to mask the unpleasant taste and secure GIT irritation.[5]

Limitations

1. Material and processing of controlled release formulation is costly than the other formations.
2. Formulations can affect or degrade polymer matrix by heat, hydrolysis, oxidation, solar radiation, or biological agent. [2]
3. The controlled release formulation of microspheres having a higher drug load and hence any loss of integrity of the release property of the formulation can lead to potential activity.
4. It should not be crushed and chewed. [3]

Types of microspheres

Bioadhesive microspheres**:** Bioadhesive microspheres are defined by the adhesive property of the water-soluble polymers. Adhesion of microspheres to the mucosal membrane Such as buccal, ocular, rectal, nasal, etc. is called bioadhesion. Bioadhesive polymers show a prolonged residence time at the site of application and show better therapeutic action.[6]

Magnetic Microspheres**:** These are tiny particles freely circulated by blood vessels without any barrier, they are sensitive so can be caught in any vessel and extravasate into the tissue through magnetic field 0.5-0.8 tesla. [7]

This type of delivery system is very useful because it delivers at the site of application. Material having magnetic property to use for preparation of microspheres, eg. Chitosan and dextran.

Magnetic microspheres are of the following types:

a. Therapeutic magnetic microspheres
   Are used to supply chemotherapeutic agent into the liver tumour. Protein and peptides are also delivered through this system.

b. Diagnostic magnetic microspheres
   These microspheres are used in imaging liver metastases as well as to pickout bowel loops from other abdominal structures through nano-sized particles supra-magnetic iron oxide.[8]

Floating microspheres: These are applicable for gastro- retentive drug delivery system and are produced by the non-effervescent approach. Microspheres defined as solid, spherical particle ranging size from 1-1000 µm. Floating microspheres are also known as micro balloons, hollow microspheres, or floating microparticles. Commonly these are free following powders prepared by protein or synthetic biodegradable polymers. The size of microspheres is small and Therefore these have a large surface area to volume ratio. Floating microspheres are spherical unoccupied particles without a core.

The Floating microspheres are designed to float on stomach fluid with low density than the stomach fluid, due to this property microspheres are delayed transit by the stomach, the dosage form is released slowly at a required rate resulting in the better gastric retention with reduced fluctuation in plasma drug concentration. [9]

Radioactive microspheres**:** These are designed to target disease sites without affecting surrounding healthy tissues.

Different radioactive microspheres α, β & γ ray emitter are ejected in arteries that are lead to the target tumour. From the target site, radioactive microspheres deliver a high radiation dose.[1]

Polymeric microspheres: These are classified into two types:- Biodegradable polymeric microspheres & synthetic polymeric microspheres.

a. Biodegradable polymeric microspheres: They are natural polymers, for eg. Starch that is biodegradable, biocompatible and bioadhesive in nature. These polymers have prolonged residence time. When contact occurs with mucous membrane, it result in the formation of a gel due to its high degree of swelling property with the aqueous medium. The extent of rate of drug release is controlled by the concentration of polymer and the pattern of drug release is in a sustained manner.
b. Synthetic polymeric microspheres: These are used in, clinical applications, further used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. These are safe and compatible but have the disadvantage that they tend to migrate away from the injection site and show potential risk, embolism, and further organ damage. [10]

Methods of preparation

The method of preparation also depends upon the nature of polymers along with drug duration and time of therapy. Following physical and chemical procedures regulate the preparation of microspheres;

1. The requirement of particle size
2. The molecular weight of polymers
3. Polymer to drug ratio
4. No stability problem
5. The final product should be non-toxic.
6. The total mass of drug and polymer
7. Reproducibility
8. Limited particle size and dispersibility in aqueous vehicles for injection, Release of the active reagent with good control over a wide time scale**.** [11]

Spray drying technique**:** The spray drying employs the technique of removal of solvent or cooling of solution. The technique has two procedures spray drying and spray congealing.

Evaporation is a basic mechanism in spray drying as well as spray phase is a phase inversion from liquid to a solid. Both procedures are the same passover for energy flow. The spray drying technique is widely used in large-scale (industrial processes) for particle

formation and drying. Therefore, spray drying is an ideal procedure for the end product to obey precise quality standards regarding particle size distribution, residual moisture content, particle shape, bulk density.

Principle: involves three following steps in spray drying:

a. Atomization**:** liquid feed converted into fine droplets.
b. Mixing**:** It involves the passing of hot gas stream over liquid which results in evaporating droplets.
c. Drug**:** Dried powder is separated from the gas stream. [2]

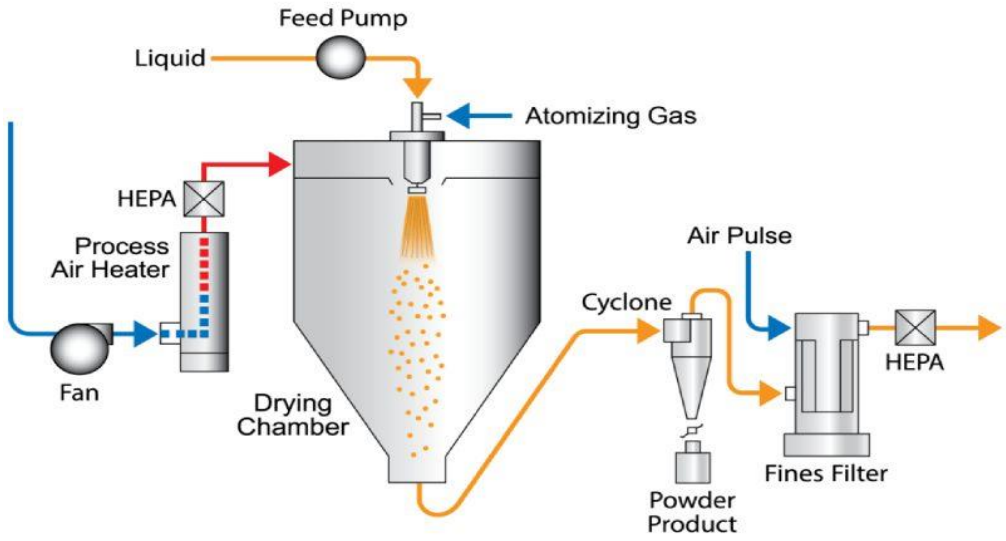

Figure 2:Diagram of spray drying technique

Emulsion- solvent diffusion technique**:** This technique is the same as the solvent evaporation technique. In the Emulsion-Solvent diffusion technique, the development of micro balloons is carried out in two steps. In the first step, the solvent is evaporated rapidly from the solvent system resulting in a hard outer layer of the emulsion and keeps the solvent inside the globules. In the second step, solvent slowly diffuses from the interior surface of the globules due to continuous stirring of the emulsion for a long time. The process creates hollowness inside the microspheres. subsequently, the hollow micronized particles are transformed into micro balloons that are separated through filtration and then dried to prepare free-flowing micro balloons. And the emulsifiers generally used are Tween 80, Span 80, and SLS. [13]

Phase separation/coacervation**:** Mainly this method is about the preparation of the reservoir type of the system. The method is used for encapsulated water soluble drugs like peptides, proteins. & preparations taking matrix type particularly when drug nature is hydrophobic like steroids. In this kind of process firstly polymer is dissolved in a suitable solvent and then the drug is dispersed through preparation it's an aqueous solution (hydrophobic) and dissolved in polymer solution itself (Hydrophilic). The phase separation is completed through change with the position by the salt addition. Change in pH, on- solvent addition and addition of the well-matched polymer. [14, 15]

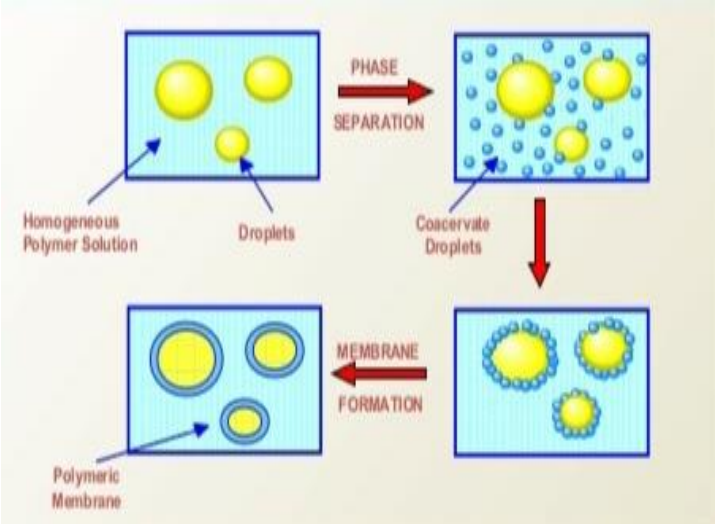

Figure 3: A diagram of phase separation/Coacervation technique

Solvent evaporation/extraction**:** This technique is performed in a vehicle containing two phases aqueous & organic phase. This process is known as emulsification. Evaporation of the solvent in o/w type emulsion results in microspheres.

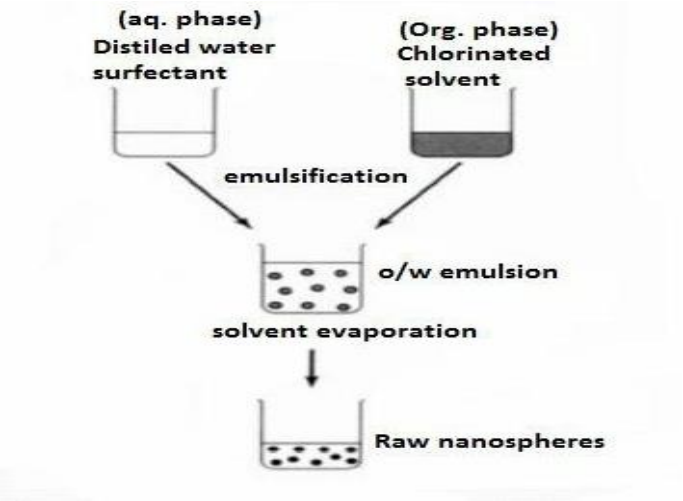

Figure 4:Steps in solvent evaporation technique

Single emulsion technique: This technique involves the aqueous solution of polymers dispersed into organic phase oil/chloroform with continuous using Sonification. after Sonification microspheres are prepared through two processes. The first one is heat denaturation and the second one is chemical cross-linking. After this procedure, the product is centrifuged, washed, and then dried to give microspheres. The cross-linking processes done by following two methods:

a. Cross linking by heat**:** in this step adding the dispersion into heated oil but these processes are inappropriate for thermolabile drugs.
b. Chemical cross-linking agent: in this step gluteraldehyde, formaldehyde, di acid chloride etc. Used as a cross linking agent. [2, 11]

Double emulsion technique**:** In this technique, the drug and aqueous polymer solution is dispersed in the organic phase which produces emulsion. Then add with the aqueous solution of PVA and prepare multi emulsion in solution followed by separation, washing, and drying the microspheres. [2]

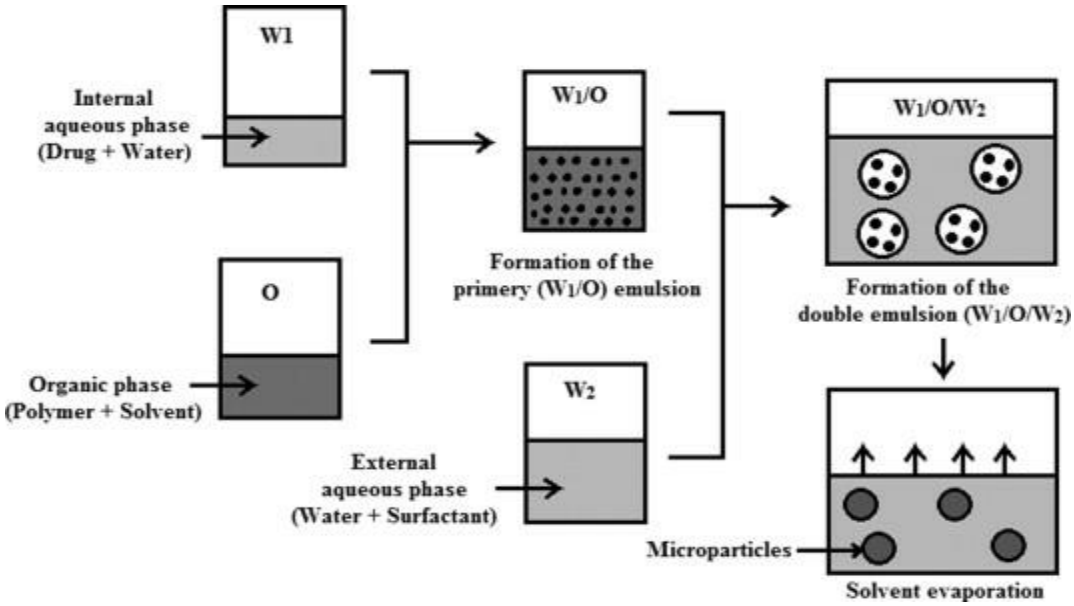

Figure 5:Double emulsion technique

Ionic gelation method**:** In this technique, 25% w/v of Diclofenac sodium is added into a 1.2% (w/v) aqueous solution of sodium alginate with continuous stirring resulting in a solution. This is added dropwise into a solution containing Ca2+ / Al3+ and chitosan dissolved into acetic acid. The resulting solution is left for 24 hours to allow gelation followed by filtration for separation. [16]

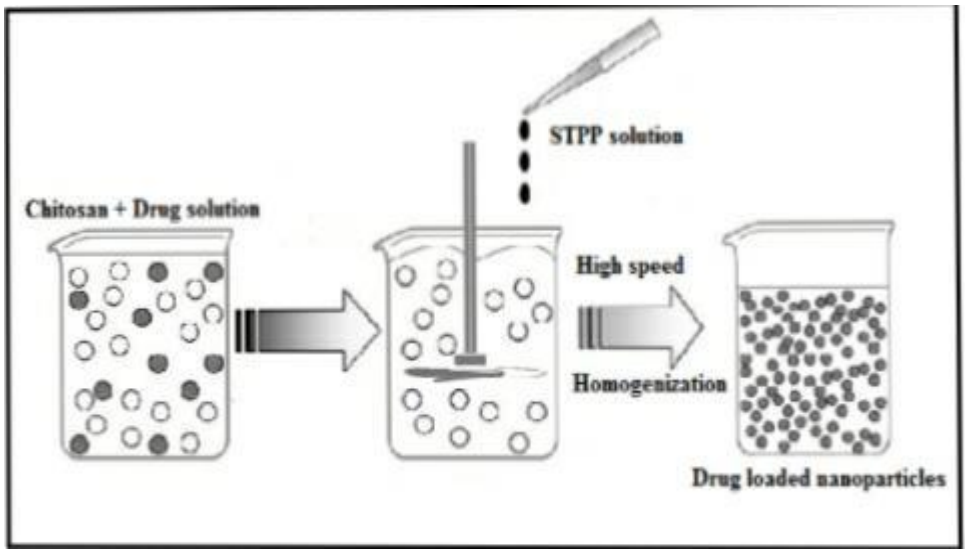

Figure 6:Steps in ionic gelation method

Evaluation of microspheres

Micromeritics properties (particle size and shape): Mostly these properties are analyzed through visualization techniques such as conventional light microscopy (LM), particle size analysis, and scanning electron microscopy (SEM).

Percentage yield**:** Percentage yield of floating microspheres is evaluated by the actual total weight of microspheres divided by the total amount of non-volatile substances that are used in the preparation of microspheres,

$$\text{Percent yield} = \frac{\text{Actual Yield}}{\text{Theoretical Yield}} \times 100\%$$

Density**:** The density is measured using multi-Pycnometer.

Iso-electric point**:** Iso-electric point is determined by the electrophoretic mobility of microspheres.[17]

Drug Entrapment efficiency**:** It is determined by the drug content of floating microspheres. The process is performed by dissolving the known amount of crushed microspheres. 0.1 N HCL is added and the solution is analysed spectrophotometrically at a specific wavelength using the calibration curve. Evaluation of every batch should be examined drug content in triplicate manner. The drug entrapment efficiency of floating microspheres is calculated by dividing the actual drug content by the theoretical drug content of microspheres.[18]

Bulk & Tap density**:** For Measurement of bulk and tap density, take a 10 ml graduated Measuring cylinder to measure the packing volume of microspheres from the cylinder. Then tap mechanically at constant velocity rotate with change in its initial bulk density to a final tap density. [19]

Swelling index**:** This method is used to measure the extent of swelling of microspheres in a particular solvent. For Measurement of the swelling of microspheres, take 5mg of dried microspheres and add with 5 ml of buffer solution, place overnight in a measuring cylinder measure and measure the mass of swollen particles.

The swelling index is calculated by following equation.[20]

formula, Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) 100.

Radiographic studies**:** In the radiographic studies, drug formulation was replaced with the same quantity of Barium Sulphate and other ingredients of formulation keep constant, microspheres were administered orally to a rabbit, radiographic images were recorded at different time intervals for 7hr. The microspheres containing $BaSO_4$ loaded Mucoadhesive microspheres are visible in the stomach for oral administration. In the initial hours, the image of microspheres is very dense but after few hours images of microspheres are lighter.[21]

FTIR study**:** In this technique the drug is mixed with potassium Bromide and pallets are prepared by compressing the powder at 100kg/cm^2 for 1 min. On KBr- press and the spectra are scanned at wave No. at 4000-400 cm^{-1}. This study was performed on drug, physical mixture of drug and polymer drug-loaded microspheres.[22]

In vitro drug release**:** In vitro drug release study using USP XXII type 2 dissolution apparatus set the temperature at 37.5°C with a rotation speed of 100 rpm. And the pipette out samples at specific time intervals and pour the same amount of fresh dissolution medium, analyze the sample at the appropriate wavelength of the drug sample using UV spectrophotometry.

Stability studies**:** For the evaluation of stability, place the microspheres into a screw-capped glass container:

1. Ambient humid condition
2. Room temperature (27±2°C)
3. Oven temperature (40±2°C)
4. Refrigerator (50°C-80°C)

It is placed for 60 days and later analyzed for drug content of microspheres.[23]

Applications of microspheres in Drug delivery

Ophthalmic Drug delivery

Microspheres are applicable in ophthalmic drug delivery and the used polymer show favorable biological behaviour like bioadhesion, permeability–enhancing properties and Physico-chemical characteristics. That creates a particular medium for ocular drug delivery vehicles due to elastic property, hydrogel gives better acceptability with the solid or semisolid formulation in the ophthalmic drug delivery eg. Like suspension or ointments. The ophthalmic chitosan gels showing adhesion property to the mucin layer, which adheres with the conjunctiva and corneal surface of the eye, and rise the Precorneal drug

residence time and the showing drug elimination time by the lachrymal flow. The addition of penetration enhancer targeted effect and permits lower doses of the drugs. In contrast, polymer-based on colloidal structures arise to work as transmucosal drug carriers facilitating the transfer of drugs into the inner eye (chitosan Nanoparticulate containing cyclosporins). The microparticulate drug carrier (microspheres) appears to encourage the topical administration of Acyclovir to the eye. Loxacin increases the efficacy timing by using the molecular weight of chitosan.[1,12]

Microspheres in vaccine delivery

The vaccine should protect against microorganisms. An ideal vaccine should fulfil the demands of safety, efficiency, satisfy the application and cost. Safety & minimization of adverse reactions is a critical issue in drug formulation. The biodegradable delivery system for vaccines given by the parenteral route may overcome the shortcoming of conventional vaccines. Microspheres in vaccines offer the following advantages: improve antigenicity by adjuvant action, modulation of antigen release stabilization of antigen.[12,16]

Medical applications

1. Protein, peptides, and hormones are released over an extended period.
2. Used in general therapy with DNA plasmid & used in insulin delivery.
3. Vaccine delivery is used to treat various diseases like hepatitis, pertussis, toxoids, ricin, influenza, birth control, diphtheria.
4. Used in tumour targeting with doxorubicin and also targeting leishmaniasis.
5. Magnetic microspheres also use to treat stem cell extraction and bone marrow purging.
6. Applicable isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.
7. Application in various, diagnostic tests for infectious disease for eg. Bacterial, fungal & viral infections.
8. The passive targeting of leaky tumour vessels, and active targeting of tumour cells and application by Intravenous and intraarterial.[16]

Microspheres used in cancer treatment

The radioactive microspheres containing β-emitter (eg. Yttrium-90) is used in the treatment of tumour in the liver. The suspension of radioactive microspheres is inserted into the hepatic artery with diameters of 30 micron which is acquired into the tumour vessels. Tumour cells become destroyed after reveal to the radiation without harming any normal or healthy cells. Polymeric microspheres having 5- fluorouracil drug used for the treatment of colon cancer. The polymeric microspheres keep safe the drug breakdown into the gastric environment.[7]

Colon specific drug delivery

These systems are used to protect the drug route to colon drug release, absorption prohibited in the stomach and small intestine. The bioactive agent should not be destroyed, released, or absorbed until it reaches the site of application. The colon-specific Tinidazole microspheres are prepared by solvent evaporation technique. Addition of Eudragit polymer and wrap up by the Eudragit microspheres as a carrier for colon targeted delivery of Tinidazole.[1]

Microspheres in gene delivery

Generally for delivery of genes recombinant Adenoviruses are used and also having high efficiency and extensive range of cell targets when use in vivo. It generates immune responses and oncogenicity as well repeated gene therapy needs when viral vectors are used. In Microspheres, non-viral gene delivery is also used to encapsulate genes and gives sustained gene delivery. Microspheres for gene delivery are prepared easily with showing stable property easily target the cell/tissue, generate low immune responses. Large-scale reproducible production is easily possible.[7,17]

Monoclonal Antibodies

These are target immune response microspheres use to reach a specific target site. Monoclonal antibodies molecule are very specific. By following methods MAbs connect into the microspheres:

non-specific adsorption and specific adsorption, Direct coupling, Coupling via reagent.[20]

Pharmaceutical Application

Various pharmaceutical microencapsulated dosage forms are present in the market, eg. Aspirin, theophylline and its derivatives, Antihypertensive, Vitamins, Pancrelipase, Progesterone, Potassium chloride, and contraceptive hormones. Microencapsulation also avoids the gastrointestinal difficulties related to Potassium chloride. The microcapsule distribution controls the release of microcapsules ions to avoid the possibility of local high salt concentration that might result in ulceration, Haemorrhage, or perforation, Inhalation, injection products are also potential applications of microspheres. Commercially available dosage form does not reflect the number of research which is carried out in this area, neither the benefits that can be availed by using this technology. The economics of encapsulation does not favour the technology as the

encapsulation process is costly and needs large initial capital funding for the equipment.

Oral drug delivery

Insulin is applicable by oral drug delivery prepared microspheres with Cyclodextrin form inclusion complex with drug molecule. The oral drug delivery of insulin is used for the treatment of diabetes mellitus. In the formulation process always use Alginate and enteric polymer to protect the degradation of the drug in the stomach or acidic environment. Chitosan Alginate membrane is used for delayed release of protein.[11]

CONCLUSION:

The microspheres are novel drug delivery systems and provide benefits such as controlled and sustained action. These microspheres can be used for ophthalmic drug delivery, various pharmaceutical application, colon drug delivery, and various medical applications such as cancer treatment, gene therapy, treatment of cell extraction, bone marrow purging, and used in several diseases like Hepatitis, Pertussis, and toxoids and infectious diseases. Microspheres offer site-specific controlled drug delivery, reduce the ordinary dose frequency, and are easy to be administered by patients. These microspheres enhance the bioavailability, stability and the sustain drug delivery gives prolonged therapeutic effect. Microspheres have some limitations such as low entrapment, loading frequency, polymer toxicity, higher cost of some dosage due to formulation time.

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