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MICROSPHERES: AS CARRIERS USED FOR NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration. A well designed controlled drug delivery system can overcome some of problems of conventional therapy and enhance therapeutic efficacy of the given drug. There are various approaches in delivering therapeutic substance to the target site in sustained and controlled release. One such approach is using microspheres as carriers for drug. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature ideally having particle size less than 200µm. This review provides brief information about mechanism of drug release, factors affecting, types of microspheres, method of preparations, evaluation and application of microspheres for controlled drug delivery.

KEY WORDS

Microspheres, Target site, Specificity, Novel drug delivery and Controlled release.

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INTRODUCTION

The word novel is searching something out of necessity. The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half life and all these leads to decrease in patient's compliance¹. To overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through

prolonged effect, adverse effect decreases by lowering peak plasma concentration. The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time².

There are various approaches in delivering a therapeutic substance to the target site in a sustained Controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 μm .

The term microspheres describe a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles³.

Drug loading and drug release kinetics⁴

The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc. Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or morphology of the carrier and the properties of the polymer itself. Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The

geometry of the carrier, i.e. whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients. In order to study the exact mechanism of drug release from the microspheres, drug release data was analyzed according to Zero-order, First-order, Higuchi square root, and Hixson Crowell and Peppas equation. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test. The zero-order kinetic (equation1) describes the systems in which the drug release rate is independent of its concentration. The first order kinetic describes the systems in which the drug release rate is concentration dependent. Higuchi described the release of drug from an insoluble matrix as a square root of the time-dependent process on the basis of Fickian diffusion. The Hixson Crowell cube root law describes the drug release from systems in which there is a change in the surface area and the diameter of particles present in the tablet. Peppas equation describes the release when more than one type of release phenomena could be involved or when the release mechanism is not well known.

$$R=k_0t \dots\dots\dots (1)$$

$$\text{LogUR}=k_1t^{2.303} \dots\dots\dots (2)$$

$$R = k_2 t^{1/2} \dots\dots\dots (3)$$

$$(\text{UR})^{1/3}=k_3t \dots\dots\dots (4)$$

$$\text{Log R} = \text{log } k_4 + n \text{ log } t \dots\dots\dots (5)$$

Where R and UR are the released and unreleased percentages, respectively, at time t. And K_0 , K_1 , K_2 , K_3 and K_4 are release rate constants for Zero order, First order, Higuchi, Hixson-Crowell and Peppas- Korsmeyer rate equations, respectively

FATE OF MICROSPHERES IN THE BODY⁵

Knowledge of the fate of microspheres after parenteral administration is very important in designing a drug delivery system. The biological fate of the administered particles has been studied by radio labeled techniques. ¹⁴C, ¹³¹I, ¹²⁵I and ⁹⁹Tc have been used for labeling. Another method for the estimation of microspheres administered into the body is by using magnetite. Magnetite estimation has the advantage that it can be easily incorporated into

the microsphere matrix by physical entrapment without altering the chemical nature of the matrix. The recovery of the microspheres from the target organs can be achieved with the aid of an atomic absorption spectrophotometer.

Mechanism of drug release

Theoretically, the release of drugs from biodegradable microspheres can be classified broadly into four different categories. But in actual practice, the mechanism is more complex and interplay of different mechanisms may operate.

Degradation controlled monolithic system

In degradation controlled monolithic microsphere systems, the drug is dissolved in the matrix and is distributed uniformly throughout. The drug is strongly to the matrix and is released only on degradation of the matrix. The diffusion of the drug is slow compared with the degradation of the matrix. When degradation is by homogeneous bulk mechanism, drug release is slow initially and increases rapidly when rapid bulk degradation starts. Drug release from such type of devices is independent of the geometry of the device. Release from a sphere is governed by the equation, where M_t is the amount of the agent released at time t , M_∞ is the amount at time t_∞ is the time for total erosion. Progesterone release from poly (glycolic-co-lactic acid) polymer films containing 10 weight% steroids is an example of this type of release.

$$M_t / M_\infty = 1 - [(1 - t / t_\infty)]^2$$

Diffusion controlled monolithic system

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Degeneration of the polymer matrix affects the rate of release and has to be taken into account. Rate of release also depends on whether the polymer degrades by homogeneous or heterogeneous mechanism.

Diffusion controlled reservoir systems

Here the active agent is encapsulated by a rare controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix. Polymer that remains as such till the complete, release of drug

and then degrades by homogenous mechanism so that the device is removed from the body is better for this type of delivery.

Targeting of microspheres

Targeting is achieved by exploiting the natural pattern of a drug carrier called passive targeting i.e. by changing the natural pattern of the carrier by some means thereby directing the drug to the specific organ or tissue. This is called active targeting.

Passive Targeting

Particles administered into the body intravenously will distribute itself in different organs depending on the size of the particles. The administered particles pass through the heart with little or no uptake to the lungs where particles $> 7 \mu\text{m}$ get entrapped in the capillary beds. Particles $< 7\mu\text{m}$ enter into the systemic circulation.

Active targeting

Active targeting includes coating the microspheres with hydrophilic cating agents which suppresses opsonization. With colloidal particles are administered into the blood streams, they may be coated with proteins such as albumin, globulin etc., depending on the nature of the material, surface charge and hydrophilicity of the particles. This is called opsonization. By coating the particles with certain polymers like poloxamer, opzonization and removal of particles by macrophages can be reduced. It is thus possible to direct particles within the body to sites such as the lung, the liver, the bone marrow or to retain them for longer periods within the systemic circulation.

Targeting using magnetic microspheres

Another approach in this area is by using magnetic microspheres. In this method magnetic loaded microspheres is infused into an artery supplying a given target site. A magnet is placed externally over the target area which restricts the microsphere to that area.

Intracellular targeting

Certain cytotoxic drugs are active intracellularly, but are normally discarded due to their poor intracellular influx. Intracellular pathogens are usually protected from the immune system and the chemotherapeutic

agents. The poor efficacy of many therapeutic substances for intracellular bacterial and parasitic therapy is well known. Commonly phagocytic cells are the sites of intracellular infection. Intracellular delivery of drugs by suitable means can obviate these problems. Albumin microspheres were avidly taken up by macrophages. They have also observed that biologically active streptomycin was released from albumin microspheres inside the phagocytic cells after ingestion and intracellular degradation of microspheres.

Factors influencing drug entrapment efficiency of microspheres⁶

Deep understanding of effects of some important factors and their interactions during the process of preparation on Microparticles physicochemical properties is necessary before designing and evaluation of microspheres.

Concentration of the polymer in dispersed phase

The particle size, swelling, loading efficiency and rate of drug release from the microspheres depended on the polymer concentration and the type of polymer used. Encapsulation efficiency increases with increasing polymer concentration. High viscosity and fast solidification of the dispersed phase contributed to reduce porosity of the microparticles as well. The contribution of a high polymer concentration to the loading efficiency can be interpreted in three ways. First, when highly concentrated, the polymer precipitates faster on the surface of the dispersed phase and prevents drug diffusion across the phase boundary. Second, the high concentration increases viscosity of the solution and delays the drug diffusion within the polymer droplets. Third, the high polymer concentration results large size of microspheres which result in loss of drug from surface during washing of microspheres is very less as compare to small microspheres. Thus size of microspheres is also affecting the loading efficiency.

Effect of concentration of emulsifier

The effect of emulsifier on the size, encapsulation efficiency and drug entrapment of the microspheres prepared using a natural polymer (bovine serum albumin) BSA using emulsification chemical cross-

linking method. Increase in concentration of emulsifier decrease the encapsulation efficiency of microspheres in some extent. This is due to fact that increase in emulsifier concentration leads to stabilization of small droplets and results in smaller microspheres. Loss of drug from surface of small microspheres is more as compared to larger microspheres during washing.

Solubility of drug in continuous phase

If the drug is more soluble in continuous phase, more drug loss in the continuous phase is occurs due to diffusion of drug from dispersed phase solubility of the drug in the continuous phase is higher than in the dispersed phase, the drug will easily diffuse into the continuous phase during this stage which tends to decrease the encapsulation efficiency.

Interaction between drug and polymer

Interaction between protein and polymer contributes to increasing encapsulation efficiency. Generally, proteins are capable of ionic interactions and are better encapsulated within polymers that carry free carboxylic end groups than the end-capped polymers. On the other hand, if hydrophobic interaction is a dominant force between the protein and the polymer, relatively hydrophobic end-capped polymers are more advantageous in increasing encapsulation efficiency. In certain cases, co-encapsulated excipients can mediate the interaction between protein and polymer.

Types of microspheres

Bioadhesive microspheres⁷

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

Magnetic microspheres⁸

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted

drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types are Therapeutic magnetic microspheres: Are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. Diagnostic microspheres can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supra magnetic iron oxides.

Floating microspheres⁹

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

Radioactive microspheres¹⁰

Radio embolisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets trapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a Radio isotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

Polymeric microspheres¹¹

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable

polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.

Method of preparation

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by Micro encapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release, method of cross linking, evaporation time and co-precipitation, etc. The various methods of preparations are:

- A. Emulsion Solvent Evaporation Technique
- B. Emulsion Cross Linking Technique
- C. Emulsion-Solvent Diffusion Technique
- D. Emulsification Heat Stabilizing Technique
- E. Ionic Gelation Technique.

A. Emulsion Solvent Evaporation Technique¹²

In this technique the drug is dissolved in polymer which is previously dissolved in chloroform and the resulting solution is added drop wise to aqueous phase containing 0.2 % of PVP as emulsifying agent and agitated at 500 rpm, then the drug and polymer solution transformed into fine droplet which solidifies into rigid microspheres and then collected by filtration, washed with demineralised water. Finally desiccated at room temperature for 24 hrs.

B. Emulsion Cross Linking Technique¹³

In this method, drug is dissolved in aqueous gelatin solution which is previously heated for 1 hr. at 40 °C. The solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 °C, which results in w/o emulsion further stirring is done for 10 min at 15 °C. Then the microspheres are washed with acetone and isopropyl alcohol. Further air dried and dispersed in 5ml of aqueous glutaraldehyde saturated toluene solution at room

temperature for 3 hrs. for cross linking and treated with 100 ml of 10M glycine solution containing 0.1%w/v of Tween 80 at 37 ° C for 10 min to block unreacted glutaraldehyde.

C. Emulsion-Solvent Diffusion Technique¹⁴

In order to improve the residence time in colon floating microparticles of drug is prepared by emulsion solvent diffusion technique. The drug polymer mixture is dissolved in a mixture of ethanol and dichloromethane (1:1) then the mixture is added drop wise to sodium lauryl sulphate (SLS) solution. The solution is stirred with propeller type agitator at room temperature at 150 rpm for 1 hr, washed and dried in a desiccator at room temperature.

D. Emulsification Heat Stabilizing Technique¹⁵

In this method, drug and polymer are dissolved in 20 ml of deionised water and 5 ml of egg albumin solution and 0.1% of Tween-80 are added stirred it for 30 min. The prepared Solution is used as aqueous phase. The oil phase is prepared by mixing 20 ml of sunflower oil and 5ml of diethyl ether with 1% span-80 (as emulsifier) and stirred it for 20 mins at 800-1000 rpm on a magnetic stirrer. The primary emulsion is prepared by adding the oil phase drop wise to the aqueous phase followed by stirring it for 30 mins at 800-1000 rpm. The prepared primary emulsion is added to pre-heated (65 to 70°C) sunflower oil (80 ml) by using 21 No. needle and stirred at 1000-1200 rpm for 2 hrs till the solidification of microspheres takes place. The suspension then allowed cooling to room temperature with continuous stirring using a magnetic stirrer. On cooling, 100 ml of anhydrous ether is added. The suspension containing the microspheres is centrifuged for 15 mins and the settled microspheres are washed three times with ether to remove traces of oil on microspheres surfaces. The obtained microspheres are then vacuumed dried in a desiccator overnight and stored at 4°C in dark.

E. Ionic Gelation Technique¹⁶

In this technique polymer is dissolved in purified water to form a homogeneous polymer solution. The core material (drug) as fine powder passed through mesh no.120 is added to the polymer solution and

mixed to form a smooth viscous dispersion. This dispersion is added drop wise into 10%w/v CaCl₂ solution through a syringe with a needle of diameter 0.55mm. The added droplets are retained in CaCl₂ solution and allowed to cure for 20 minutes at 200 rpm to produce spherical rigid microsphere. Finally the microspheres are collected and dried in an oven at a temperature 45°C for 12 hrs.

Evaluation of microspheres

The microspheres are evaluated by the following tests:

Particle size analysis

Particle size distribution of the microspheres can be determined by optical microscopy using calibrated ocular eyepiece.

Drug entrapment efficiency¹⁷

Microspheres containing drug (5mg) are crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hrs, and filtered then assayed by UV-visible spectroscopy.

$$\text{Entrapment efficiency} = \frac{\text{actual drug content}}{\text{theoretical drug content.}}$$

Scanning electron microscope (SEM) study¹⁸

The surface morphology and particle size of microspheres are determined by Scanning Electron Microscopy. Dry microspheres are placed in a scanning electron microscope brass stub and coated with gold in an ion sputter. Picture of microspheres are taken by random scanning.

In vitro drug release study¹⁹

The drug release study are performed using USP dissolution test apparatus paddle type at 37 ± 0.5°C and at 100 rpm using 900 ml of phosphate buffer pH 7.4, as dissolution medium for 8 h. Microspheres equivalent to 10 mg of drug are used for the test. 5 ml of sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably, and analyzed spectrophotometrically at suitable nm. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample.

Stability studies²⁰

By placing the microspheres in screw capped glass container and stored them at following conditions:

1. Ambient humid condition

2. Room temperature (27+/-2 °C)
3. Oven temperature (40+/-2 °C)
4. Refrigerator (5 °C -8°C).

It was carried out of a 60 days and the drug content of the microsphere was analyzed.

Zeta potential²¹

The polyelectrolyte shell was prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles were determined by zeta potential measurement.

Pharmaceutical applications of microspheres²²

- Gene therapy with DNA plasmids and also delivery of insulin.

- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertussis, ricin toxoid, diphtheria, birth control.
- Tumor targeting with doxorubicin and also treatments of leishmaniasis.
- Used in isolation of antibodies, cell separation and toxin extraction by affinity chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial/ intravenous application.

Table No.1: Marketed Products²

S.No	Trade Name	Generic Name	Sponsor
1	Madopar	Levodopa floating CR capsule	Roche Products, USA
2	Valrelease	Diazepam floating capsule	Hoffmann-LaRoche, USA
3	Liquid Gaviscon	Al hydroxide Mg carbonate Effervescent floating liquid alginate preparation	Glaxo Smith Kline, India
4	Topalkan	Al-Mg antacid floating liquid alginate preparation	Pierre Fabre Drug, France
5	Convicon	Ferrous sulphate colloidal gel forming FDDS Gas-generating floating tablet	Ranbaxy, India
6	Cifran OD	Ciprofloxacin colloidal gel forming FDDS	Ranbaxy, India
7	Cytotec	Misoprostol bilayer floating capsule	Pharmacia, USA
8	Oflin OD	Ofloxacin gas releasing floating tablet	Ranbaxy, India

CONCLUSION

It has been observed that the microspheres are better choice of drug delivery system because it is having advantage of target specificity and better patient compliance. A number of methods have been devised to prepare microspheres of desired size shape and surface. Compare to other Novel drug delivery system, Microspheres have better choice for drug delivery system, particularly in diseased cell sorting, diagnostic of gene, targeted and effective *in-vivo* delivery. So in feature; microspheres will have an important role to play in the advancement of medical field.

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