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REVIEW ARTICLE

FORMULATION AND EVALUATION OF MICROSPHERE: AN OVERVIEW

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ABSTRACT

Microspheres constitute an important part of novel drug delivery system by virtue of their small size and efficient carrier capacity. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm. The range of Techniques for the preparation of microspheres offers a Variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. 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 also known as micro particles. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs. The purpose of the review is to compile various types of microspheres used in the formulation of microsphere drug delivery system and its applications.

Keywords: Microspheres, controlled release, target site, novel drug delivery

INTRODUCTION

Microspheres are small spherical particles, with diameters 1 µm to 1000 µm. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix. Solid biodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products.

Arthritis is a major syndrome affecting majority of the geriatric patients and generally NSAID'S are advised to reduce pain and inflammation[1]. The medications prescribed for the relief of inflammation and associated pain are available as conventional dosages like tablets and capsules. The conventional medications cause GI disturbances and drug level fluctuates considerable making the patients to suffer or the patients is burdened with overdosage[2.] To minimize the GI

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disturbances and to improve the bioavailability of the drug certain novel dosage forms and being investigated. In the past two decades there has been a commendable growth both in size and to improve bioavailability and patient compliance. Transdermal drug delivery systems(TDDS) are designed to support the passage of drug substances from the surface of skin, through its various layers, into the systemic circulation. Their advantages over conventional dosage form include improved patients compiance, avoidance of gastric irritation and first pass effect and controlled therapeutic responces[3].

Advantages[5,6]

1. To improve bioavailability.
2. To improve the stability.
3. Improving patient compliance.
4. Decreasing dosing frequency.
5. Self-life enhancement by preventing degradative reactions.
6. Better processability(improving solubility,dispersibility,flowability).
7. Safe and convenient handling of toxic materials.
8. Protection of unstable, sensitive materials from their environments prior to use.
9. Enzymes and micro-organism immobilization.
10. Controlled and targeted drug delivery.

Disadvantages[6]

1. The modified release from the formulations.
2. Controlled release formulation generally contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
3. Dosage forms of this kind should not be crushed or chewed.
4. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
5. Differences in the release rate from one dose to another.

Components[7,8]

A number of different substances both biodegradable as well as non biodegradable have been investigated for the preparation of microsphere.

Core material

• Drug or active constituent
• Additives like diluent
• Stabilizers
• Release rate enhancers or retardants

Vehicle

1. Aqueous
2. Non Aqueous

Coating material

• Inert polymer
• Plasticizer
• Coloring agent
• Gelatin, gum Arabica, methyl cellulose, beeswax, carnauba wax

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MATERIALS: A number of different substances both biodegradable & non biodegradable has been investigated for the preparations of microspheres. These materials include the polymers of natural and synthetic origin and also modified natural substances.

A. **SYNTHETIC POLYMERS**[8,9,10,11]

1) **Non-biodegradable polymers**
- PMMA(polymethylmethacrylate)
- Acrolein
- Glycidyl methacrylate
- Epoxy polymers

2) Biodegradable polymers
- Lactides and glycosides and their copolymers
- Polyalkyl cyano acrylates
- Polyanhydrides

B. NATURAL POLYMERS[12-14]

1. Proteins
- Albumin
- Gelatin
- Collagen

2. Carbohydrates
- Starch
- Agrose
- Carragenen
- Chitosan

TYPES OF MICROSPHERES

1. **Magnetic microspheres:** 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[15-16]: 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 supramagnetic iron oxides.

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2. **Radioactive microspheres[17-18]:** Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So in all these conditions radcioactive 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 radioisotope typical distance and the different kinds of radioactive microsphers are α emitters, β emitters, γ emitters.

3. **Bioadhesive microspheres:** 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[19].

4. **Floating microspheres:**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 gasteric contentand 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.[20-21]

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

6. **Synthetic polymeric microspheres:** The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolismand further organ damage[22-23].

7. **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[24].

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METHOD OF PREPERATIONS[25,26,27]

1) **Single Emulsion Technique: -** The natural polymers are dissolved or dispersed in aqueous or non-aqueous medium followed by dispersion in the non aqueous medium e.g. oil. Than cross linking of the dispersed globules is done by the means chemical cross linkers glutaraldehyde, formaldehyde, teraphthaloyl chloride etc. After centrifugation, washing and separation the microspheres can be obtained.
2) **Double Emulsion Technique:-** In this technique multiple emulsions of o/w or w/o is formed. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. The primary emulsion thus formed is subjected to homogenization before the addition to aqueous solution of poly vinyl alcohol. This results in the formation of multiple emulsions. This emulsion is then subjected to solvent removal or extraction. This results in the formation of microspheres.
3) **Polymerization Technique:** In this technique, a dispersion is made by using active material and the aqueous solution of NaOH with surfactant medium. After heating the above system polymerization occurs which on settling forms microspheres.
4) **Phase Separation Technique:** In this technique, the polymer is first dissolved in a suitable solvent and then the drug is dispersed by making its aqueous solution. Than the phase separation is induced by the techniques like addition of incompatible polymer or change of ph etc. As a result polymer rich globules are formed which get harden after some time. On separation the microspheres are formed.
5) **Spray Drying and Spray Congealing:** In this technique the polymer is first dissolved in a suitable volatile organic solvent like acetone, dichloromethane etc. The drug in the solid form is than dispersed in the polymer solution. This dispersion is than atomized in a stream of hot air. The atomization leads to the formation of the small droplets from which the solvent evaporates instantaneously leading the formation of the microsphere.
6) **Solvent Extraction Technique:** The solvent extraction technique depends on the removal of the organic phase by extraction of the organic solvent. The organic solvent used is isopropyl alcohol and the organic phase is removed by extraction with water. The therapeutic benefit of microencapsulated drugs and vaccines brought forth the need to prepae such particles in larger quantities and in sufficient quality suitable for clinical trials and commercialisation. Our findings will be outlined according to the four major substeps of microsphere preparation by solvent extraction/evaporation, namely,

- Incorporation of the bioactive compound.
- Formation of the micro-droplets.
- Solvent removal.
- Harvesting and drying the particles.

EVALUATION OF MICROSPHERES[28-32]

1. **% yield of microspheres:** Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formula given below,

    a. % Yield = mass of microsphere obtained / total weight of drug & polymer X 100
2. **Particle size analysis:** Particle size distribution Particle size determination was done by sieving method. Size distribution plays an important role in determining the release characteristics of the microspheres.

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3. **Angle of repose:** Angle of repose was determined by using funnel method. The accurately weighed microspheres were taken in a funnel and then height of funnel was adjusted in such as way that the tip of funnel just touches the apex of heap of blends. The blends were allowed to flow through funnel freely on to surface. The diameter of powder cone was measured and angle of repose was calculated by using following equation.

    i. $\tan\theta = h/r$

    b. Where
    c. θ – Angle of repose,
    d. h –height of pile,
    e. r – Radius of base.

4. **Determination of drug content: Accurately** weighed 100 mg microspheres were crushed in glass mortar and pestle, powder microspheres were suspended in 100 ml of suitable solvent. After 12 hours the solution was filtered and the filtrate was analyzed for the drug content using UV-Visible spectrophotometer.

5. **Encapsulation efficiency:** Encapsulation efficiency was calculated using the following formula; E = Qp / Qt X 100

    Where, E = percentage of encapsulation of microspheres
    Qp = quantity of drug encapsulated in microspheres
    Qt = quantity of the drug added for encapsulation

6. **Swelling studies: A** known weight (50 mg) of microspheres was placed in a glass vial containing 10 ml of distilled water at 37 ± 0.50C in incubator with occasional shaking. The microspheres were periodically removed, blotted with filter paper and their changes in weights were measured during the swelling until equilibrium was attained. Finally, the weight of the swollen microspheres was recorded after a period of 3 hours, and the swelling ratio (SR) was then calculated from the following formula. The studies were carried out in triplicate.

    SR=We-Wo / Wo
    Where,
    Wo = Initial weight of the dry microspheres,
    We = Weight of the swollen microspheres at equilibrium swelling in the media.

7. **In vitro dissolution studies: Dissolution** studies were carried out for the microspheres, employing USP XXIII apparatus (Basket method) at 37± 0.5 0C rotated at constant speed of suitable rpm using suitable dissolution medium. A sample of microspheres equivalent to 100 mg of loaded microspheres was used in each test. An aliquot of the sample was periodically withdrawn at suitable time interval and the volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The sample was analyzed spectrophotometrically at suitable nm.

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8. **Carr's index:** It was measure by using following formula,
   a. Carr's Index = {(Vb –Vt) / Vb}* 100
   b. Where,
   c. Vb and Vt are the bulk volume and tapped volume respectively.

FACTORS INFLUENCING PROPERTIES OF MICROSPHERES

1. **Polymers commonly used to form microspheres.**
2. **Choice of solvent.**
   - It should be able to dissolve the chosen polymer.
   - Poorly soluble in the continuous phase.
   - High volatility and a low boiling point.
   - Low toxicity.
   - Alternative components (Dispersed Phase).

   a) Co-Solvent: The organic solvents miscible with water such as methanol and ethanol.

   b) Porosity generator: It will increases the degradation rate of polymer and improves drug release rate.

3. **Continuous phase.**

   a) Surfactant

- It reduces the surface tension of continuous phase.
- Avoids the coalescence and agglomeration of drops.
- Stabilizes the emulsion.

APPLICATIONS OF MICROSPHERES

The brief outline of various applications of microsphere is explained as follows[33-34]

1. Microspheres in chemotherapy[6]

The most promising application of microspheres are possible to used as carriers for anti- tumor agents. Enhanced endocytic activity and leaky vasculature administrated microspheres. Stealth microspheres are prepared by coating with soluble polyoxy ethylene. The accumulation of non-stealth microspheres in Reticulo Endothelial System (RES) may also be exploited for cancer chemotherapy[35-36].

2. Microspheres for DNA Delivery [37]

Microspheres have been recently used as a delivery vehicle for the transfer of plasmid DNA which leads to improve the transfer of plasmid DNA and their stability in the bio- environment. Truong-Le & Co workers (1998) developed a novel system for gene delivery based on the use of DNA-gelatin microspheres/ nanoparticles formed by salt induced complex coacervation of gelatin & plasmid.

3. Fluorescent microspheres

These are made up of polystyrene or poly vinyl toluene, mono disperse system ranging in size from 20nm to 4µm. Preparation of fluorescent microspheres comprising, swelling the polymeric

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microsphere so that fluorescent dyes may enter the microsphere pores. Unswelling the polymeric microspheres so that the fluorescent dyes become physically entrapped in the pores.

4. Adjuvant effect for vaccines

An adjuvant effect of the microspheres/nanoparticles with either matrix entrapped or surface adsorbed vaccines have been demonstrated in several studies on substances or oral administration. "Kreuter & Co-workers" observed that Poly methyl methacrylate microspheres containing the influenza antigen induced significant antibody response. Oral delivery of antigens with microspheres may be an elegant means of producing an increase Immunoglobin A (Ig A) antibody response.

5. Microspheres for Ocular delivery

The most applications of drug loaded ophthalmic delivery systems are for glaucoma therapy, especially cholinergic agonists like pilocarpine. The short elimation half life of aqueous eye drops can be extended from a very short time (1-3 min) to prolonged time (15-20 min) using microspheres which have biodegradable properties eg: Poly alkyl cyano acrylate.

6. Microspheres for Lymph targeting

The major purpose of lymph targeting is to provide an effective anticancer chemotherapy to prevent the metastasis of tumor cells by accumulating the drug in the regional lymph node. Example: Poly alkyl cyanoacrylate microspheres bearing anticancer drugs for tumor of peritoneal cavity. Poly (lactide-co-glycolide) microspheres for the lymphatic of diagnostic agents.

Medical application [37-38]

- Release of proteins, hormones and peptides over extended period of time.
- 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.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra-arterial/ intravenous application.
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- 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.

CONCLUSION

This review article covers all related microsphere system including their application. Microsphere has been prepared using different method.

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