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A MODERN REVIEW ON MICROSPHERE AS NOVEL CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

Microspheres are spherical and free flowing particles ranging in average particle size from 1 to 50 microns which consist of proteins or synthetic polymers. Some of the problems overcome by producing control drug delivery system which enhances the therapeutic efficacy of a given drug. One such approach is using microspheres as carriers for drugs. The target site drug delivers with Specificity and maintains the concentration at site of interest without untoward effects. It will find the central place in novel drug delivery. Drugs can be targeted to specific sites in the body using microspheres. Degree of targeting can be achieved by localization of the drug to a specific area in body (for example in lungs), to a particular group of cells (for example, kupffer cells) and even to the intracellular structures (as lysosomes or cell nucleus). The rate of drug release from the microspheres dictates their therapeutic action. Release is governed by the molecular structure of the drug and the polymer, the resistance of the polymer to degradation, and the surface area along with the porosity of the microspheres.

KEYWORDS

Microspheres, Target site, Controlled release, Novel drug delivery and Therapeutic efficacy.

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INTRODUCTION

Microspheres have played a vital role in the development of controlled/sustained release drug delivery systems[1]. Microspheres have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and controlled drug release. Microspheres are matrix systems that contains drug throughout their structure and are potential candidates for oral controlled release. Microsphere can be defined as solid spherical particles

ranging from one to 1000μm in size[2]. A controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion[3].

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration[4]. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion[5]. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. Polyethylene and polystyrene microspheres are two most common types of polymer microspheres[6].

Advantages of Microspheres[7-12]

- They facilitate accurate delivery of small quantities of potent drug and reduce concentration of drug at site other than the target organ or tissue.
- They provide protection for unstable drug before and after administration, prior to their availability at the site of action.
- They provide the ability to manipulate the *in vivo* action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug.
- They enable controlled release of drug. Examples: Narcotic, Antagonist, Steroid hormones.
- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
- Improved receptor activation selectivity Extended time over critical (effective) concentration.
- Less inter- and intra-subject variability.
- Flexibility in dosage form design.
- Improves patient compliance by decreasing dosing frequency.
- Better therapeutic effect of short half-life drugs can be achieved.
- Gastric retention time is increased because of buoyancy.
- Drug releases in controlled manner for prolonged period.
- Enhanced first-pass biotransformation.
- Sustained drug delivery/reduced frequency of dosing.
- Targeted therapy for local ailments in the upper GIT.
- Site-specific drug delivery to stomach can be achieved.
- Enhanced absorption of drugs which solubilize only in stomach.

Carriers used in Preparation of Microsphere[13, 14, 15]

The following are the polymers used in the preparation of microspheres.

Synthetic polymers

- Non-biodegradable polymers: Poly methyl methacrylate (PMMA), Glycidylmethacrylate, Epoxy polymers.
- Biodegradable polymers: Lactides, their glycolides and their copolymers, Polyalkyl Cyano Acrylate, Polyanhydrides.

Natural polymers

These are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

- **Proteins:** Albumin, Gelatin, and Collagen,
- **Carbohydrates:** Agarose, Carrageenan, Chitosan, Starch,
- **Chemically Modified Carbohydrates:** Poly (acryl) dextran, Poly (acryl) starch.

Types of Microspheres

Bio adhesive Microspheres[7,16,17]

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 Microspheres[16,18]

Magnetic microspheres are supra molecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4μm) but are sufficiently susceptible (ferromagnetic) to be captured in micro vessels and dragged into the adjacent tissues by magnetic field of 0.5-0.8 tesla.

Floating Microspheres[9,16,19]

Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period without affecting gastric emptying rate. The drug is released slowly at the desired rate.

Radioactive Microspheres[16,20]

Radioactive microspheres deliver high radiation dose to the targeted are as without damaging the normal surrounding tissues. They are injected to the arteries that lead to tumour of interest. The different kinds of radioactive microspheres are α emitters, β emitters and γ emitters.

Polymeric Microspheres[16,21]

Biodegradable polymeric microspheres are those which contain biodegradable polymers which 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. Synthetic polymeric micro spheres are those which are made up of synthetic polymers and are used as used as bulking agent, fillers, embolic particles, drug delivery vehicles etc.

METHODS OF PREPERATION

Single emulsion technique[13,16]

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved/dispersed in aqueous medium followed by dispersion in the non-aqueous medium e.g. oil. In the second step of preparation, cross-linking of dispersed globule is carried out. The cross linking is achieved by two methods i.e. either by heat or by means of chemical cross linking agents including glutaraldehyde, formaldehyde, diacid chloride etc.

Double emulsion technique[13,16,22]

This method involves the formation of the multiple emulsion or double emulsion of type w/o/w. It is best suited to water soluble drugs, peptides, proteins and vaccines. This method can be used with both the natural as well as the synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in formation of a double emulsion. Emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction process. The solvent evaporation is carried out by maintaining emulsion at reduced pressure or by stirring the emulsion so that the organic phase evaporates out. The emulsion is then added to large quantity of water into which organic phase diffuses out. The solid microspheres are subsequently obtained by filtration and washing with n hexane, acetone or any organic solvent to remove traces of oil from the surface.

Polymerization[13,16,23]

The polymerization techniques conventionally used for the preparation of the microspheres, are mainly classified as:

Normal polymerization

Interfacial polymerization

Normal polymerization[24]

Normal polymerization proceeds and is carried out using different techniques as bulk, suspension

precipitation, emulsion and micellar polymerization processes. In bulk polymerization, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers

Interfacial polymerization[25]

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed, one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase.

Phase separation/ Coacervation[13,25]

Phase separation method is mainly designed for preparing the reservoir type of the system. This method is used to encapsulate water soluble drugs e.g. peptides, proteins and some of preparations having matrix type particular, when the drug is hydrophobic in nature e.g. steroids. In this technique the polymer is first dissolved in a suitable solvent and then drug is dispersed by making its aqueous solution, if hydrophobic or dissolved in polymer solution itself, If hydrophobic. Phase separation is then accomplished by changing the solution conditions by the salt addition, on-solvent addition, addition of the incompatible polymer or change in pH.

Spray drying[13, 26]

The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of microspheres.

Solvent extraction[1]

Solvent extraction method is used for the preparation of the micro particles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. The process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion

volume to the water and the solubility profile of the polymer.

Emulsion Solvent Evaporation[13,27,28]

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with

Demineralized water and desiccated at room temperature for 24 hrs.

Emulsion solvent diffusion technique[13,29]

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

PHYSICOCHEMICAL EVALUATION

Characterization

Particle size and shape[30,31]

Light microscopy (LM) provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically Scanning electron microscopy (SEM) allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems.

Attenuated total reflectance FT-IR Spectroscopy[30, 32]

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The ATRFT-IR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

Density determination[30]

The density of the microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the density of the microsphere carrier is determined.

Isoelectric point[30]

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined.

Entrapment efficiency[30,33]

Microspheres containing of drug (5mg) were crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr., and was filtered then assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content. % Entrapment = Actual content/Theoretical content x 100

Swelling index[34]

This technique was used for Characterization of microspheres were performed with swelling index technique Different solution (100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37℃ and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.

Angle of contact[30]

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or Hydrophobicity. The angle of contact is measured at the solid/air/water interface. The angle of contact is measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres.

Modified Keshary Chien Cell[30,35,36]

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 370℃ as 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.

Dissolution apparatus[30]

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using rotating elements, both paddle and basket. Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

Animal models[30]

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 In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the esophagus is ligated to prevent absorption pathways

other than oral mucosa. At different time intervals, the blood is withdrawn and analyzed.

Stability studies[30,37]

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

- Ambient humid condition
- Room temperature (27+/-2℃)
- Oven temperature (40+/-2℃)
- Refrigerator (5℃ -8℃). It was carried out of a 60 days and the drug content of the microsphere was analyzed.

Applications of Microspheres in Pharmaceutical Industry

- For taste and odour masking.
- To delay the volatilization.
- For Separation of incompatible substances.
- For Improvement of flow properties of powders.
- To Increase the stability of the drug against the external conditions.
- For Safe handling of toxic substances.
- To improve the solubility of water insoluble substances by incorporating dispersion of such material in aqueous media.
- To reduce the dose dumping potential compared to large implantable devices.
- For conversion of oils and other liquids to solids for ease of handling.

Novel Applications of Microspheres[13]

Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies (Mabs) targeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting at specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be used to target microspheres loaded bioactive molecules to selected sites by means of covalent coupling. The free amino groups, aldehyde groups, or hydroxyl groups on the external surface of the microspheres can be linked to the antibodies. Attachment of microspheres to Mabs by any of the following methods.

1. Non-specific adsorption
2. Specific adsorption
3. Direct coupling
4. Coupling with reagents.

Targeting by using micro particulate carriers

The concept of targeting, i.e. site specific drug delivery is a well-established dogma, which is gaining full attention. The therapeutic efficacy of the drug depends on its access and specific interaction with its candidate receptors. Placement of the particles indiscrete anatomical compartment leads to their retention either due to the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.

Microspheres in vaccine delivery

The prerequisite of a vaccine is protection against micro-organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, convenience in application and cost. The aspect of safety and minimization of side effect is a complex issue. Biodegradable delivery systems for vaccines that are given by i v route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies because they offer specific advantages including:

1. Modulation of antigen release
2. Improved antigenicity
3. Stabilization of antigen.

Topical porous microspheres

These micro sponges are having capacity to entrap wide range of active ingredients such as emollients, fragrances, volatile oils etc., are used as the topical carries system furthermore, these porous microspheres with active medicaments can be incorporated into formulations such as creams, lotions and powders. .

Surface modified microspheres

Different approaches have been used to change the surface properties of carriers to protect them against phagocytic clearance and to modify their body distribution patterns. The adsorption of poloxamer on surface of the polystyrene, polyester or poly methyl methacrylate microspheres deviate them more hydrophilic and hence they decrease their MPS uptake. Protein microspheres can be covalently modified by PEG derivatives show decreased immunogenicity and clearance.

CONCLUSION

Microspheres form an important drug delivery strategy for controlled release and targeting. Microspheres containing anti-neoplastic drugs, steroid hormones, vaccines, proteins and peptides, antiviral, antifungal and antibiotic drugs, anti-diabetic drugs and anti-inflammatory drugs are investigated extensively for controlled release by various routes and for targeting. In recent years studies on microspheres have been increased as it has become a promising technology in the areas of drug delivery, proteomics and genomics and also for studying bio molecular interactions.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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