ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

REVIEW ARTICLE

A Review on Microsphere

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ABSTRACT

Microspheres are characteristically free flowing powders having particle size ranging from 1-1000 µm consisting of proteins or synthetic polymers. 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. 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. Moreover the microspheres are of micron size so they can easily fit into various capillary beds which are also having micron size. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs. There are various departments of medicine like cancer, pulmonary, cardiology, radiology, gynecology, and oncology etc., numerous drugs are used and they are delivered by various types of drug delivery system. Among them microspheric drug delivery system has gained enormous attention. The purpose of the review is to compile various types of microspheres, different methods to preparation, its applications and also various parameters to evaluate their efficiency.

Key words: Microsphere, types of microsphere, preparation, application.

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ISSN: 0975-8585

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.

Microspheres are sometimes referred to as microparticles. 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. Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immuno precipitation. Proteins and ligands adsorb onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments. Polyethylene microspheres are commonly used as permanent or temporary filler. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. High sphericity of polyethylene microspheres, as well as availability of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences, process troubleshooting and numerous research applications. Charged polyethylene microspheres are also used in electronic paper digital displays. Glass microspheres are primarily used as filler for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology. Ceramic microspheres are used primarily as grinding media. Microspheres vary widely in quality, sphericity, uniformity of particle and particle size distribution. The appropriate microsphere needs to be chosen for each unique application.

MATERIALS AND METHODS

Materials used [4-9]

Different polymers are used in microspheres. They are classified into two types:

Synthetic polymers are divided into two types.
Non-biodegradable polymers

e.g. Poly methyl methacrylate (PMMA)
Acrolein
Glycidyl methacrylate
Epoxy polymers
Biodegradable polymers
e.g. Lactides, Glycolides & their co polymers
Poly alkyl cyano acrylates
Poly anhydrides

Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.
Proteins:

e.g Albumin, Gelatin, and Collage

Carbohydrates:

e.g Agarose, Carrageenan, Chitosan, Starch

Chemically modified carbohydrates:

e.g Poly dextran, Poly starch.

Ideal criteria [10]

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and
- Susceptibility to chemical modification.

Types of microsphere [11-13]

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.

ISSN: 0975-8585

Magnetic microspheres

This kind of delivery system is very much important which localises 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 type 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 supramagnetic iron oxides.

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. Drug (ketoprofen) given through this form.

Radioactive microspheres

Radio embolization 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 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.

Polymeric microspheres

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 treatement.

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, embolism and further organ damage.

Method of preparation [9, 10, 14, 15,]

- Single emulsion technique
- Double emulsion technique
- Polymerization technique
- Normal polymerization
- Interfacial polymerization
- Phase separation coacervation technique
- Spray drying and spray congealing
- Solvent extraction
- Quassi emulsion solvent diffusion
- Wax coating & hot melt

Single emulsion technique

There are several Proteins and carbohydrates, which are prepared by this technique. In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e. non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods

Cross linking by heat: by adding the dispersion into heated oil, but it is unsuitable for the thermolabile drugs.

Chemical cross linking agents: by using agents i.e. formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) is added to Liquid paraffin containing a surfactant resulting formation of w/o emulsion. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent.

Double emulsion technique

It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put a t constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e. formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e. multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and drying and collection of microspheres1 genistein chitosan microsphere were prepared by the o/w/o multiple emulsion method.

Polymerization techniques

Mainly two techniques are using for the preparation of microsphere are classified as:

Normal polymerization

In bulk polymerization, a monomer or a mixture of number 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 by adding the drug during the process of polymerization. It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermo labile active ingredients. Suspension polymerization is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less the 100 µm. Emulsion polymerization is differ from the suspension as due presence of initiator in aqueous phase but is also carried out at low temperature as suspension external phase normally water in last two techniques so through which heat can easily dissipate .formation of higher polymer at faster rate is possible by these techniques but association of polymer with the un reacted monomer and other additives can occur.

Interfacial polymerization

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 is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet.

Phase separation coacervation technique

It is the simple separation of a micro molecular solution into two immiscible liquid phases. In this process, the polymer is solubilized to form a solution. This process is designed for preparing the reservoir type system e.g. encapsulate water soluble drugs i.e. peptides, proteins etc. The principle of coacervation is decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, formation of dispersion of drug particles in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Matrix types preparations can also be prepared by this process for hydrophilic drug e.g. steroids, addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. But this method is not suitable for organic solvents and glutaraldehyde which are toxic in nature.

Spray drying and congealing

Spray drying and spray congealing methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or the cooling of the solution, the two processes are named spray drying and spray congealing respectively. 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 lead to the formation of small droplets or the fine mist from which the solvent evaporates leading to the formation of microspheres in a size range 1-100µm. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying.

Solvent extraction

Solvent evaporation method is used for manufacturing of microparticles, involves removal of the organic phase by extraction or non-aqueous solvent. This method involves water miscible organic solvents as isopropanol. Organic phase can be removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. Rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer.

Quassi emulsion solvent diffusion

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase is consisting of drug, ethanol

and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60ºC and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40ºC for a day.

Wax Coating and Hot Melt

In this technique polymer is disperse in suitable dispersion medium and slowly cooled to form the microspheres. The polymers which having low melting point fabricated into microspheres by this technique easily. For coating and coring of particle wax is use mostly. In which encapsulate the drug by dispersion in the molted wax. The wax suspension is dispersed by high speed mixing into cold solution for example liquid paraffin. Agitate the mixture for one hour. Then decanted the external phase and suspended microspheres collect from solvent. And allow drying it in air. It is inexpensive method as comparison to others and drug release is more rapid. Mostly Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics.

Characterization / evaluation of microspheres [13, 16]

Particle size analyzer

Microsphere (50 mg) was suspended in distilled water (5mL) containing 2%w/v of tween 80. To prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometer.

Optical microscopy

This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye piece and 45x objective) and100 particles were calculated.

Scanning electron microscopy (SEM)

Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slub with the help of double sided sticking tape and coated with gold film under reduced pressure.

Swelling index

This technique was used for characterization of sodium alginate 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 alginate microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed

at 37oC 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.

UV-FTIR (Fourier transform infra-red)

The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR.

Stability studies

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

Ambient humid condition

Room temperature (27 +/-2oC)
Oven temperature (40 +/- 2oC)
Refrigerator (50oC - 80oC)

It was carried out of a 60 days and the drug content of the microsphere was analysed.
In vitro method

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and in vivo techniques have been reported. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physicochemical and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations; however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed. The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using overhead stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.
Application of microspheres [13]

Medical application

- 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.
- Other applications:
- Fluorescent microspheres can be used for membrane based technologies for flow cytomettry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay.
- Yttrium 90 can be used for primary treatment of hepatocellular carcinoma and also used for pretransplant management of HCC with promising results.

CONCLUSION

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumours, detecting bimolecular interaction etc. so in future microspheres will have an important role to play in the advancement of medicinal field.

REFERENCES

[1] SP Vyas and RK Khar. Targeted and Controlled Drug Delivery: Novel Carrier System 1st edition. CBS publication and distributors, New Delhi, 2002, 81-121

[2] Thanoo BC, Sunny MC, Jayakrishnan A. J Pharm Pharmacol 1992; 44: 283-286.

[3] Sarvana K, Jayachandra R, Chandrashekhar K. Journal of Pharmacy Research 2012; 5(1): 420-424.

[4] Kreuter J, Nefzger M, Liehl E, CzokR, Voges R. J Pharm Sci 1983; 72: 1146.

[5] Margel S, WieselE. J Polym Science Polym Chem Ed 1984; 22: 145-158.

[6] Wakiyama N, Juni K, Nakano M. Chem Pharm Bull 1981; 29: 3363-3368.

[7] Sugibayashi K, Akimoto M, Moromoto Y, Nadai T, Kato Y. Pharmacobiodyn 1979; 23: 50.

[8] Yoshioka T, Hashida M, Muranishi S, Sezaki H. Int J Pharm 1981; 81: 131-141.

[9] Alagusundaram M, Madh sudana C, Umashankar K. Int J Chemtech Research 2009; 1(3): 526-534.

[10] Nirav P, Dhagash P, Praful B, Vikaram P and Dharshan N. Intr J Pharma Life Sci 2011; 2(8): 992-997;

[11] Patel JK, Patel RP, Amin AF, Patel MM, http://www.pharmainfo.net/reviews/ bioadhesivemicrospheres-review. Retrieved 2012-12-16.

[12] Physics and Chemistry Basic of Biotechnology. Focus on biotechnology. Review. Radioactive Microspheres for Medical Application, http://www.springerlink.com/ content/r883r91q17576vx6/. Retrieved 2012-11-25
[13] Prashantha VV, Akash CM, Sam TM, Rink M. International J Research Pharma Biomed Sci 2011; 2(2): 332-338.
[14] Harsh B, Simar K, Atul G. Int J Pharma Sci Review and Research 2011; 10(1): 69-78.
[15] Amol C, Jadhav KR, Kadam VJ. Int J Pharma Sci Review and Research 2010, 5(1), 8-17.
[16] Sahil K, Akanksha M, Premjeet S, Ajay B, bhawani K. Int J Research Pharma Chem 2011; 1(4): 1184-1198.