

Review Article

Microspheres - A New Drug Delivery System: A Review

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Abstract

Microspheres are normally free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and preferably having a particle size less than 200-500 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 different approaches in delivering a therapeutic substance to the target site in a sustained controlled release manner. 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 customized, and to maintain the desired concentration at the site of significance. Microspheres established much attention not only for extended release, but also for targeting of anticancer drugs. In future by combining various other strategies, microspheres will find the central place in new drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

Keywords: Microspheres, extended release, target site, new drug delivery.

1. Introduction

An extended drug delivery system can solve some of the problems of old therapy and improve the healing efficacy of a given drug. To obtain highest healing efficacy, it becomes necessary to deliver the agent to the target tissue in the best possible amount in the right period of time there by causing little toxicity and negligible side effects. There are approaches in delivering a therapeutic substance to the target site in a sustained extended release manner. One such approach is using microspheres as carriers for drugs¹. The drug has to be delivering for an expanded stage of time and many medicines have to be taken simultaneously in case of chronic patients. Regular administration of drug is required when those have shorter half life and all these leads to decrease in patient's compliance.

In order to overcome the above troubles, 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 release the drug at a predetermined rate for an extended period of time. One such in Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system. Microspheres are defined as "massive sphere or healing agent dispersed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level². Microcapsules are those in which entrapped material is particularly bounded by distinct capsule wall and micrometrics in which entrapped material is dispersing throughout

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the microspheres matrix. Solid ecological 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 products³.

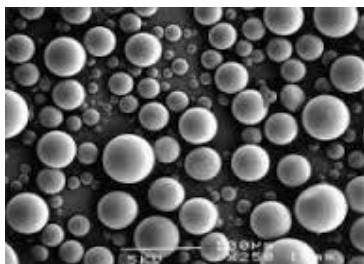


Fig.1: Microspheres.

2. Types of Microspheres

2.1. Bioadhesive microsphere

Adhesion can be defined as sticking of drug to the membrane by means of the sticking assets of the water soluble polymers. Adhesion of drug delivery tool to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. These kinds of microspheres show a prolonged residence time at the site of application and causes warm contact with the absorption site and produces better healing action⁴.

2.2. Magnetic microspheres

This type of delivery system is very much significant which localizes the drug to the disease Site. In this superior amount of generously 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 transport chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be besieged through this system.

Diagnostic microspheres: Can be used for imaging liver metastases and also can be used to

Differentiate bowel loops from other abdominal structures by forming nano size particles Supramagnetic iron oxides⁴.

2.3. Floating microspheres

In this type of microsphere bulk density is less than bulk density of gastric fluid so that it remain floating in the stomach without affecting the gastric emptying time. Drug is released slowly at the desired rate, the system is floating on gastric substance and increases gastric dwelling and increases variation in plasma absorption. It also reduces chances of striking and dose dumping. Single another way it produces extended healing effect and therefore reduces dosing frequencies⁵.

2.4. Polymeric microspheres

There are different types of polymeric microsphere which can be classified as follows.

- i) Biodegradable polymeric microspheres
- ii) Non-Biodegradable polymeric microspheres

i) Biodegradable polymeric microspheres

Starch is used as biodegradable biocompatible polymer and bioadhesive in nature. Biodegradable polymer prolongs the residence time when come in contact with mucous membrane due its high degree of swelling property with aqueous medium results in to gel formation. The drug release is controlled by concentration of polymer and release pattern in controlled manner⁵.

ii) Synthetic polymeric microspheres

Synthetic polymers are widely used in clinical applications also used as bulking agent, fillers, embolic particles, drug delivery vehicles and proved to be safe and biodegradable. Main drawback of these kinds of microspheres is tend to migrate away from site of application and cause risk and organ damage⁵.

2.5. Diagnostic microspheres

Diagnostic microspheres are used for imaging the liver metastases and also can be used to differentiate bowel loops from abdominal structures by formation of nano size particles supramagnetic iron oxides⁵.

2.6. Radioactive microspheres

Radioactive microspheres are useful for many therapy once the encapsulated diagnostic radioisotopes has been exchanged for

therapeutics from the- or β -emitter group. It is used for treatment of rheumatoid arthritis, liver tumors and cystic brain tumors. However, their use remains experimental because of smaller than expected target uptake, unwanted toxicity and insufficient treatment effects that have resulted from radio chemical instability and suboptimal biodistribution of the radiopharmaceutical⁶.

3. Method of Preparation

Different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation etc. There are various methods of preparations which are as follows.

3.1. Emulsion solvent evaporation technique

In this method the drug is dissolved in polymer which was earlier dissolved in chloroform and the resultant solution is added to aqueous phase containing 0.2 % sodium of pvp as emulsifying agent. The beyond mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transferred into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs.

3.2. Emulsion-solvent diffusion technique

The drug polymer combination is 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 stimulated with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a dessicator at room temperature. The following Microparticles were sieved and collected.

3.3. Emulsion cross linking method

In this method drug was dissolved in aqueous gelatin solution which was previously heated for 1 hr at 40 0C. The elucidation was added drop wise to liquid paraffin while stirring the

mixture at 1500 rpm for 10 min at 35^{0c}, results in w/o emulsion then additional stirring is done for 10 min at 15 ^{0c}. Thus the produced microspheres were washed correspondingly three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glycine solution containing 0.1%w/v of tween 80 at 37 0 C for 10 min to block unreacted glutaraldehyde.18 Examples for this technique is Gelatin A microspheres⁷.

3.4. Phase Separation Coacervation Technique

This method is based on the principle of decreasing the solubility of the polymer in organic phase to affect the development of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is further added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer⁸.

3.5. Spray Drying and Spray Congealing

The polymer was first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form was then dispersed in the polymer solution under high speed homogenization. This dispersion was then atomized in a stream of hot air. The atomization leads to the development of the small droplets or the fine mist from which the solvent evaporate instantly leading to formation of the microspheres in a size range 1-100 μ m. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively⁸.

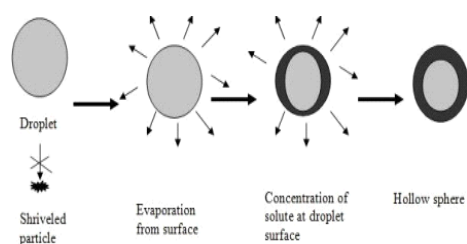


Fig.2: Formation of product in spray drying.

3.6. Wet Inversion Technique

Chitosan solution in acetic acid was drop in to an aqueous solution of counter ion sodium tripolyphosphate through a nozzle. Microspheres produced were permitted to stand for 1 hr and cross linked with 5% ethylene glycol diglycidyl ether. Microspheres were then washed and freeze dried. Altering the pH of the coagulation medium could modify the pore structure of CS microspheres. Complex Coacervation CS microparticles can also prepare by complex co acervation, Sodium alginate, sodium CMC and sodium polyacrylic acid can be used for complex coacervation with CS to form microspheres. These microparticles are formed by interionic interaction between oppositely charged polymers solutions and KCl & CaCl₂ solutions. The obtained capsules were hardened in the counter ion solution before washing and drying⁹.

Polymer	Polymer
Modified starch, HPMC, Carbopol 974P	Modified starch, HPMC, Carbopol 974P
Ethyl Cellulose	Controlled release for longer period of time.
PLGA, Chitosan	Vaccine delivery.
PLA, Starchcyanoacrylate etc(PEG-) liposomes.	Drug delivery without toxic side effects.
Magnetic polystyrene microspheres	Specific cell labelling.
Polymer resins such as Agarosepolyacrolone, sephadex	Affinity chromatography.
Chitosan coated PIGA microspheres	Targeted drug delivery
Polyvinyl alcohol, polyacrylamide	Polyvinyl alcohol, polyacrylamide

Table 1: Various types of polymers and their application⁷.

4. Advantages of Microspheres

- It protects the unstable and sensitive material from prior environment.
- It improves solubility, dispersibility and flow ability.
- It is helpful for safety handling of toxic material.
- To improve the bioavailability.

- To improve the therapeutic efficiency of drug.
- To improve the stability of drug.
- Helpful for masking of odor and taste of drug.

5. Applications of Microspheres

- Microsphere is most useful for the preparation of tablets, capsules or parenteral dosage forms.
- Microsphere can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach.
- It can be used to mask the taste of bitter drugs.
- It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat.
- The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation.
- Microsphere can be use to reduce the volatility. An encapsulated volatile substance can be stored for longer times without substantial evaporation.
- The hygroscopic properties of many interior materials may be reduced by microsphere.
- Many drugs have been microsphere to reduce gastric irritation.
- Microsphere technique has also been proposed to prepare intrauterine contraceptive device¹⁰.

6. Drug loading in Microsphere

Actually drugs are overloaded in the microspheres mainly using two methods i.e. during the grounding of the microsphere or after the grounding of the microsphere by incubating them with the drug solution. The active ingredient may be loaded by means of the physical entrapment, chemical linkage and surface absorption. It was found that highest drug loading in microspheres may be achieved by incorporating the drug through the time of preparation but it may get affected by many other process variables like presence of additives, method of preparation, heat of polymerization, agitation intensity etc.

The loading of drug following the preparation of microspheres may be achieved by incubating them with high concentration of the drug in a appropriate solvent. Here drug may be loaded in the microspheres through penetration or diffusion of the drug through the pores present in the microsphere as well as by absorption of drug on the surface of microspheres. The solvent is then detached, leaving drug-loaded microsphere¹¹.

7. Compatibility Studies for reformulation

7.1. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is one of the spectroscopic analysis used to identify the compatibility studies between the drug and excipients. Therefore the study is always carried out using FTIR using SHIMADZU-FTIR 410 model.

7.2. Differential Scanning Calorimetric (DSC)

DSC analysis is carried out to identify the compatibility study between the drug and excipients. The DSC analysis of pure drug, 1:1 physical mixture of drug and excipients were carried out using mettler Toledo DSC 821, Switzerland. Samples (2-8 mg) were accurately weighed and heated in sealed aluminum pans at a rate of 10⁰c/min between 0-300⁰C temperature ranges under nitrogen atmosphere¹².

8. Evaluation of Microspheres

8.1. % yield of microspheres

Dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formula given below,
 % Yield = mass of microsphere obtained / total weight of drug & polymer X 100

8.2. Particle size analysis

8.2.1. Particle size distribution

Particle size fortitude was done by sieving method. Size distribution plays an important role in decisive the release characteristics of the microspheres.

8.3. Angle of repose

Angle of repose for microsphere was determined by using funnel method. The correctly weighed microspheres were taken in a funnel and then height of funnel was

accustomed 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 equation¹².

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

Where

θ – Angle of repose,

h –height of pile,

r – Radius of base.

8.4. Capture efficiency

The capture effectiveness of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:

$$\% \text{ Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$$

8.5. Angle of contact

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.

8.6. Drug release

In vitro methods

In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product formulation etc. Sensitive and reproducible release data derived from physic-chemically and hydro dynamically defined conditions are necessary, 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.

8.6.1. Beaker method

The dosage form in this technique is made to adhere at the bottom of the beaker containing

the suitable medium and stirred consistently using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm¹².

8.6.2. Modified Keshary Chien Cell

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

8.7. Drug content estimation

The drug content of microsphere can be determined according to I.P. The absorbance was measured and percentage of drug content can be calculated from it¹².

8.8. Dissolution rate.

Standard USP or BP dissolution apparatus can used to study in vitro release profiles using rotating elements, paddle and basket. Dissolution intermediate used for the study varied from 100-500 ml and speed of revolution from 50-100 rpm¹³.

8.9. Swelling index

This method was used for description of microspheres were carried out with swelling index method. Different solution 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°C 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^{13,14}.

Conclusion

Microsphere is a specific drug delivery system used to deliver the drug to targeted site for therapeutic efficacy, and if modification is done in this microsphere to maintain desired concentration at the site of application. In the microsphere drug is located in the central part of the particle. Microsphere is used now days for various treatments for controlled release of drug. In future definitely microsphere will find the central place in the drug delivery system.

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