Pakistan Journal of Pharmaceutical Research
Faculty of Pharmacy, Bahauddin Zakaryia University Multan, Pakistan
ISSN: Applied January, 2015 Vol: 01 Issue: 01

Review Article

Microspheres: a potential carrier for Drugs

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Received: 14 Oct 2014
Revised: 25 Dec 2014
Accepted: 28 Dec 2014
Online: 31 Dec 2014

Abstract

Micro particles are one of the recent controlled release dosage form, compressed in the form of tablets or filled in capsules for the delivery of drugs. In this review different methods of preparations and their effects on physical properties i.e. size, shape and porosity which can be controlled by ingredients used or process variables and characterization will be discussed. Future dimensions of these dosage forms are numerous when it comes to its application in drug delivery and to overcome issues associated with new drug molecule in drug discovery process.

Keywords: Microspheres, Polymers, Microencapsulation

Introduction:

A conventional oral dosage forms does not usually provides rate controlled release at target site. sometimes it provides sudden increase in drug concentration which leads to toxic levels (Freiberg and Zhu, 2004). With advances in combinatorial synthesis of materials, bio-material sciences and micro sciences, there are a number of opportunities available to address the issues related to drug development like drug solubility, potency, efficacy and stability (Kriwet et al., 1998; Lucas and Astorga, 2006). There is always a need of safer and more effective drug delivery system that minimises the physicochemical and pharmacological barriers of a drug molecule. Different approaches are being employed, which include control and sustained release tablets, nano and micro particles synthesis, injectable and inserts, that introduce the drug in systemic circulation.

Traditional tablets and capsule dosage forms directly exposed to acidic environment (Win et al., 2005), while microspheres may be used to protect the drug from acidic environment. Micro particulate drug development strategy offers a lot of opportunities in dosage form (Li et al., 2008) and currently getting a lot of attention. Microspheres are small spherical particles, sometimes referred to as micro particles ranging from 1-1000 µm. Microspheres can be compressed in tablets or filled in capsules but they have their own advantages when administered as such (Makino et al., 2000).

Most of building materials emerging for Micro particle synthesis are polymeric in nature. Although other natural materials like gums, cellulose derivatives or lipids are also under

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consideration for the preparations of microspheres. In this review different methods of preparations of microspheres like solvent evaporations, emulsion cross linking, coaceravations and spray drying will be discussed in detail. Different hydrophilic and lipophilic polymers will be used for encapsulation of both type of drugs either weakly acidic or basic. Different characterizations like scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), X ray diffraction (XRD) and differential scanning calorimetry (DSC) will also be explained. Applications of microspheres in the field of drug delivery and its effect like dosage form will also improve the concepts of readers.

Materials and Methods

Preparation of Microspheres

Different methods were used to get the desired size, shape, porosity, drug loading and pharmacological/biopharmaceutical properties in the final Micro-preparations.

Solvent evaporation

Most commonly employed technology at lab level is solvent evaporation (O'Donnell and McGinity, 1997). Polymers solution or dispersion is emulsified in an aqueous continuous phase to form droplets. The organic solvent evaporates at water / air interface, harder and free flowing microspheres are obtained after suitable filtration and drying (Spenlehauer et al., 1989). Choice of solvent is according to the solubility of the polymers i.e. Polyvinyl alcohol in water and Poly lactide-co-glycolic acid in ethyl acetate, poly lactic acid in acetone and poly-caprolactone and poly anhydrides in methyl chloride. Polyvinyl alcohol can also be used as emulsifying agent due to its amphiphillic property (Spenlehauer et al., 1989). Sonication or homogenization and amount of emulgent affect the size of microspheres. Once emulsion subjected to drying, there is no control on size (Bodmeier and McGinity, 1988). Drying achieved via stirring evaporation i.e. aqueous phase remained in the beaker with particles suspended in it. Another approach was via freeze drying in which freezing before drying can affect the size or even can destroy the particles but it can be addressed by using cryoprotectant like dextrose or sucrose(Bozdag et al., 2005). In this case both water and oil phase removed leaving behind the particles. The droplets become enrich with ingredients and polymer at the surface. It solidified afterwards and become dried particles. Different process variable like stirring, drying speed, solvent type and amount of ingredients have been reviewed earlier. Briefly it was found that increase in the dispersing agent concentration can decrease the particle size like in case of hydroxypropyl methylcellulose, the concentration was increased from 0.4 to 2.4 % and particle size was reduced from 5.8 µm to 3.2 µm. This method was used for water soluble/ insoluble, proteins and vaccine delivery (Alex and Bodmeier, 1990).

The disadvantage of this method is that uniform size of particles is not achieved and also not reproducible. It is economical only at lab scale but not at industrial or commercial level. However a method was proposed to generate the uniform sized microspheres. It utilizes sophisticated nozzle jet which combine the drug and polymer solution into a particle with polymer at the outer layer and drug inside, at uniform rate and then spray it in a uniform droplet form(Kim and Pack, 2006).

Emulsion cross linking method

In this method, the cross linking of polymers were controlled via reaction conditions. The rest of method was almost same as that of solvent evaporation. Starch based microspheres were prepared via this method (Malafaya et al., 2006). Trisodiumtrimetaphosphate was used as cross linker. Starch and cross linker were dissolved in water phase which were emulsified with drug solution in organic solvent. Emulsifier of both hydrophilic i.e. Tween 20 and of hydrophobic nature i.e. Span 20 were used to prepare water in oil and oil in water emulsions. The cross linker was activated via basic condition i.e. pH 12-13 with NaOH solution. Reaction was stopped by neutralizing the condition with HCl and microspheres were centrifuged and washed to separate them from oil phase.

Disadvantage of this method was that the particles obtained at the end were not well defined in shape and cross linking was done even across the particles, so different aggregates were obtained (Malafaya et al., 2006).

Co-acervation method

In this method polymer and drug solution was made in the organic solvent to make organic phase. Another solution of polymer was made in the water. Phase separation was carried out by adding the aqueous phase into the organic phase drop wise under high speed stirring. The particles were coacerved upon dripping and separated via centrifugation, air dried and characterized. Enteric release microparticles were prepared by this method. HPMC and poloxamer were dissolved in aqueous layer with PH 7.4 buffer while eudragit and drug were dissolved in organic phase i.e acetone / ethanol (1:1) (Dong and Bodmeier, 2006).

Ion gelation method

The preparation of microspheres by the complexation of oppositely charged macromolecules has attracted much attention because the process is very simple. Lee, et al. prepared the microspheres by using internal gelation method, in which calcium carbonate was used as a source of calcium ions. Aqueous solution of various amounts of calcium carbonate was made and added in to the solution of sodium alginate. Then this mixture was added to the organic solvent containing span 85 and stirred for 10 minutes by using mechanical stirrer. Galacial acetic acid was then added to release calcium ions from calcium carbonate, so that calcium ions react with alginate to produce microspheres (Silva et al., 2006). These particles are utilized for their application in tissue regeneration and as support in tissue engineering(Chan et al., 2002).

Spray drying

Spray drying is a common technique to produce powders or granules from mixture of drug and polymer solution or suspension. This method was based on drying of atomized droplets in a stream of hot air. In this method polymer was dissolved in aqueous acetic acid solution, drug was dissolved or dispersed in it and then a cross linker was added. The solution or dispersion was then atomized in a stream of hot air. Atomization leads to the formation of small droplets from which solvent evaporates leading to the formation of free flowing micro particles(Agnihotri et al., 2004).

He, et al (He et al., 1999) Prepared both uncross linked and cross linked microparticles by spray drying method.

Conti, et al (Conti et al., 1998) Produced microparticles by exposing spray dried particles to the vapors containing cross linking agents.

Ganza, et al (Agnihotri et al., 2004) Produced microparticles by spray drying method using formaldehyde as cross linker.

Lorenzo-Lamosa, et al (Lorenzo-Lamosa et al., 1998) Prepared microencapsulated chitosan microspheres for colonic delivery of Diclofenac Sodium by using spray drying method.

Characterization of Microspheres

Usual physical characterization of microspheres include, size and shape. Size of large particles are obtained via optical microscopy while those at smaller level i.e. 1-10 µm are visualized via electron microscopy. Due to burning of sample beneath electron beam, particles are usually coated with some metallic solution to visualize them. Shape and surface texture of microspheres are examined by Scanning electron microscopy (SEM).

Drug encapsulation efficiency is determined via UV-visible spectrophotometer. FTIR is performed to evaluate the drug stability by identification of characteristics functional peaks in pure and formulation form. Stability studies are also performed by placing them in accelerated stability conditions and monitoring the drug degradation pattern via UV-visible spectrophotometer or even mass spectrometry in order to observe the degradation products of drug at different conditions in different formulations.

Applications of Microspheres engineering in Drug Delivery technology

All these polymeric fabrication and optimization of microspheres are directed toward safe and effective drug delivery. Different solutions to the problems provided by microspheres are as follows.

Biodegradability of Microspheres

Microspheres are prepared by using biodegradable ingredients. Polymer is major ingredient of this formulation beside drug, so it should be biocompatible and biodegradable. Polylactic acid, polyglycolic acid, co polymers of these two, polyvinyl alcohol are examples of biodegradable polymers. These are even used as building blocks to prepare further functional polymers. Different ratios blend of these polymers are injected in experimental animals and observed for any sign of discomfort, inflammation and wound healing process. Degradation and indirect toxic species are also monitored in blood along with other blood biochemical parameters. Even polymers obtained from natural origin like glycosidic polymers or those obtained from Aloe species are also good candidates as biodegradable polymers.

Micro particles fabricated via these polymers are easy to stay silent in biological systems. Surface of these particles are further modified to be bio-silent by using polyethylene glycol systems which are silent for immune systems.

Proteins and Vaccines delivery

Proteins and vaccines are bio-sensitive molecules which cannot be given orally. They are sensitive to acidic environment of gut. To protect and deliver them intact, they are encapsulated inside various polymer fabricated micro systems. Examples include interleukins, thyrotropins, insulin and even hormones releasing in controlled manner from these particles. Similarly anti cancer agents

sensitive to be given orally, are also entrapped inside these systems.

Controlled release

Control of drug release from the microspheres mostly depends upon the cross linked polymer or pores formed by them on the surface of particles. Single dose hepatitis B vaccine was developed by entrapping them inside Poly lactide and glycolide polymers. They were not immune disturbing and characterized to be completely biocompatible (Singh et al., 1997). It provided single dose plasma levels for one year which were equal to those provided by three injections of standard conventional formulation of same vaccine. Similarly same polymers in blend with polyethylene glycol were used to encapsulate and control release of hypoglycemic drugs for optimum control over blood glucose levels with single oral dose (Jain et al., 2005). Short half-life drugs like lornoxicam and artemether are also getting benefits from control release profile of polymer micro particles.

Conclusion

The microencapsulated particles of various polymers can be used for different diseases with high drug entrapment efficacy which minimize the toxic effect of the drug. These can be obtained by use of biodegradable polymer which degrades in body with no harmful effects. These microencapsulated particles can be prepared by solvent evaporation, emulsion cross linking, ion-gelation, coacervation and spray drying methods. Use of microencapsulated particles is a recently developed technique for latest medicine like interleukins, thyrotropins, insulin and even hormones releasing in controlled manner from these particles.

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