Asian J. Pharm. Res. Vol 3, Issue 2, 99-102, 2013.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

MICROSPHERES AS DRUG DELEVERY SYSTEMS-A REVIEW

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ABSTRACT

Microspheres offer the possibility of local noninvasive delivery of drugs over an extended period of time. Biologically adhesive delivery systems offer important advantages ^{over} conventional drug delivery systems. Here we show that engineered polymer microspheres made of biologically erodable polymers, which display strong adhesive interactions with gastrointestinal mucus and cellular linings, can traverse both the mucosal absorptive epithelium and the follicle-associated epithelium covering the lymphoid tissue of Peyer's patches. The polymers maintain contact with intestinal epithelium for extended periods of time and actually penetrate it, through and between cells. Thus, once loaded with compounds of pharmacological interest, the microspheres could be developed as delivery systems to transfer biologically active molecules to the circulation. Thus it has proved to be better alternative for the formulation of several drugs. In this review it has clearly mentioned about the different methods for the formulation of microspheres along with their evaluation methods.

Key words: micro spheres, drug loading, drug release.

INTRODUCTION

Microspheres are spherical empty particles. Microcapsules are spherical with size varying from 50 nm to 2 mm containing a core substance. Some related terms are Micro beads and Beads are used alternatively. Micro beads are large size and rigid morphology.

The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200µm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug. These are used for controlled release and targeted drug delivery eg: Drug to the tumour [1].

Materials used

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspores. These materials include the polymers of natural and synthetic origin and also modified natural substances. Synthetic polymers employed as carriers materials are methyl methacrylate, acrolein, lactide, glycolide and their copolymers, ethylene vinyl acetate copolymer, poly anhydrides etc. The natural polymers used for the purpose are albumin, gelatine, starch, collagen and carrageenan etc.

Prerequisites for ideal micro particulate carriers

- Longer duration of action
- Controlled of content release
- Increase of therapeutic efficacy
- Protection of drug
- Reduction of toxicity
- Bio-compatibility
- Sterilizability
- Relative stability
- Water solubility or dispersability
- Bioresorbability
- Target ability [2,3].

General methods of preparation

The method of preparation and its choice are equivocally determined by some formulation and technology related factors as mentioned below:

- The particle size requirement
- The drug or the protein should not be adversely affected by the process

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- Reproducibility of the release profile and the method
- No stability problem
- There should be no toxic product associated with the final product.

Methods of preparation

- Solvent evaporation method:
- Hot melt method
- Solvent removal method
- Single and double emulsion method
- Spray methods
- Freeze drying method

1. Solvent evaporation method

- Oldest and widely used method of microspheres preparation.
- In this method drug/polymer/solvent mixture (i.e., the oil phase) is emulsified in water in order to form an oil in water emulsion.
- To assist emulsification a surfactant is normally dissolved in the water phase before the O/W emulsion is formed.
- A good example is partially hydrolysed (88%) polyvinyl alcohol.
- Once the desired oil phase droplet size and emulsion stability have been obtained, the system is stirred at a constant rate and the solvent evaporates

2. Hot melt method

- The melted polymer mixed with the drug. The mixture is then suspended in an immiscible solvent and it is heated at 5^0C above the melting point of the polymer.
- This mixture is stirred with a four blade impeller once the emulsion is stabilized; it is cooled until the core material is solidified.
- The solvents used in this process can be silicon and olive oil.

3. Solvent removal method

- In this method fabrication occurs at room temperature and totally in organic solvent, which is an important consideration for hydrolytically labile polymers such as polyanhydrides.
- In this method the polymer is dissolved in methylene chloride, desired amount of drug is added then the mixture is suspended in silicon oil, span 80, methylene chloride [4,5].
- After pouring the polymer solution into the silicon oil, petroleum ether is added and the mixture is stirred until the methylene chloride is extracted from the oil solution and sufficient hardening of microspheres is achieved.
- The resulting microspheres are separated by filtration, washed with petroleum ether and dried over night under vacuum.
- The size of microspheres is always smaller than 300µm [6,7].

4. Single and double emulsion method

- The most common method is double emulsification method i.e., W/O/W.
- The aqueous protein solution is dispersed in an organic solvent consisting of polymer solution to obtain a W/O emulsion.
- This unstable emulsion is then stabilized by further emulsification in aqueous solution of dispersing agent.
- After the removal of the organic solvent the polymer is precipitate out forming tiny spheres containing the dispersed phase.
- In single emulsion method the microspheres of natural polymers carbohydrates are prepared by using glutareldehyde as cross linking agent.

5. Spray methods

- The basic principle involved is to dry the drug and polymer in the air.
- In this method spray drying, spray congealing is there.
- In spray drying polymer solution is prepared with a volatile organic solvent (acetone).
- Drug is dispersed and homogenized and this mixture is atomized in the stream of hot air.
- In spray congealing method cooling of the polymer solution is done [8,9].

6. Freeze drying method

- It involves the freezing of emulsions.
- The relative freezing points of the continuous and dispersed phases are important.
- The continuous phase solvent is usually organic and is removed by sublimation at low temperature and pressure.
- The dispersed phase solvent of droplet is removed by sublimation leaving polymer drug particles as microspheres.

Some other methods are

- ❖ Wax coating method.
- ❖ Chemical and thermal cross linking method.
- ❖ Coaservation phase separation method [10,11].

Drug loading

- Water soluble drug molecules are added to the polymer solution and are incorporated with stirring up to 10% W/W drug can be entrapped in the micro particles.
- Optimum drug loading can be achieved by incorporating drug during the preparation of microspheres. This method is influenced by the process variables such as additives, heat of polymerization.
- The second consists of combining the drug with the polymer matrix via covalent bonds and shaping them into small particles.

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- The drug loading in the microspheres after formation is less as compared to the drug loaded during microspheres preparation.

Mechanism of drug release

➢ **Diffusion control drug delivery**

These are spherical polymer matrix devise containing dispersed drug molecules either in solution or in crystalline form. They cannot move away from matrix. The drug can elute out of the matrix first by dissolving in the surrounding polymer and then diffusing through the polymer structure.

➢ **Hydrolysis –Activated drug delivery**

This type of drug release depends on the hydrolysis process. All these systems are prepared by polymer such as poly anhydrides. The release of drug from a polymer matrix is activated by the hydrolysis induced degradation of polymer chains and controlled by the rate of polymer degradation.

➢ **Enzyme activated drug delivery**

This type of drug release depends on enzymatic process of some enzymes in the target tissue. For example albumin microspheres that release 5-fluorouracil in a controlled manner by protease activated bio degradation [12,13].

Classes of microspheres

▪ **Chitosan microspheres**

These are generally prepared with solution of chitosan in aqueous acetic acid containing NaCl and this solution is dispersed in a mixture of liquid paraffin and petroleum ether containing sorbitan sesquioleate in a round bottom flask. This is stirred using a stainless steel half-moon paddled stirrer at 1000rpm for some time and gluteraldehyde saturated toluene is introduced into the flask and stirring continued. The hardened microspheres are filtered and washed with petroleum ether followed by methanol, sodium bisulphate and finally with acetone and dried [14,15].

▪ **Floating microspheres**

These are used for the development of controlled release of the drug. This causes the increase in the residence time in stomach.

Characterization

Micrometrics

The shape and topography of surface of the microspheres are observed by using SEM or TEM. Size and size distribution is by using laser diffraction particle size and analyzer. The surface charge by zeta meter. Inside structure of microspheres is by co focal laser scanning microscopy. The hollow structure of micro balloons is estimated by measuring the particle density by two methods.

- Photographic counting method
- Liquid displacement method.

Drug entrapment and content

By DSC the m.p and crystal heat are measured with a DSC.

Drug entrapment = practical drug content/theoretical drug content X 100

Drug release

The loaded microspheres is weighed accurately and suspended in the dialysis tube. The release behaviour drug from system is tested at 37^0C in PH 7.4 phosphate buffer for 12 hours at 100rpm. Amount is estimated by using UV spectrometry or HPLC.

Mucoadhesive microspheres

By using rat stomach mucosa

$N_a = (N/N_0)*100$ [16-18].

CONCLUSION

Pharmaceutical applications

- Currently marketed products are aspirin, theophylline and its derivatives, vitamins, pancreolipase, anti-hypertensive, KCl, progesterone and contraceptive hormone combinations.
- Microencapsulated potassium chloride is to prevent gastro intestinal complications.
- Used as antigen carrier.
- Used in inhalation or injection products.
- Used to develop the taste masking sulpha drugs, alkaloids.

Therapeutic applications

- Targeted to specific sites in the body using microspheres.
- Toxic vaccine microsphere were effectively delivered and released in the gut associated lymphoid.
- Bio adhesive microspheres have boosted the use of bio adhesion in drug delivery.

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