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POLYMERIC MICROSPHERES: A REVIEW

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ABSTRACT
Over the conventional therapy, the novel drug delivery systems have much advantages. In the recent trends the microparticulate drug delivery are especially suitable for achieving the controlled or delayed release oral formulations. Oral formulations have risk of dose dumping, poor bioavailability and short gastric residence time. One such approach is using microspheres as delivery system; a well-designed controlled release system can overcome problems related to conventional therapy. Microspheres can enhance the therapeutical efficacy of particular drug. Microspheres are free flowing powder consisting of natural or synthetic polymers which are biodegradable in nature. Microspheres ideally having a particle size less than 500 µm. Microspheres received much attention not only for the prolong drug release but also for targeting release of certain drugs in severe diseases like cancer. Microspheres as delivery system offers numerous advantages, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. This review article highlights various types of microspheres, method of preparations, its advantages and evaluation parameters to check its efficiency.

KEYWORDS: Conventional, Microspheres, Controlled Release, Targeted Release, Patient Compliance, Bioavailability, Dose Dumping, Microparticulate, Polymer, Biodegradable.

INTRODUCTION

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. There are two types of microspheres.

- **Microcapsules**
- **Micromatrices**

Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall.
Micromatrices in which entrapped substance is dispersing throughout the microsphere's matrix.

Polymeric Microspheres

The different types of polymeric microspheres can be classified as followed 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 prolong the residence time when contact 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.

Synthetic Polymeric Microspheres

The interest of synthetic polymeric microspheres is widely used in clinical application as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible.[1]

the polymers used in the preparation of microspheres further classified into two types.

Synthetic Polymer

Synthetic polymers are divided into two types.
a) Non- biodegradable polymers - Poly methyl acrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers.
b) Biodegradable polymers - Lactides, Glycolides& their copolymers, Poly alkyl cyanocrylates, Poly anhydrides.

Natural Polymers

The natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumins, Gelatin, Collagen.

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch.

Chemically modified carbohydrates: Poly (acryl) dextran, Poly (acryl) starch.

Preparation of microspheres should satisfy certain criteria

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

METHOD OF PREPARATION

Emulsion Solvent evaporation technique

In this technique the processes are carried out in a liquid manufacturing vehicle. In this process the microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core.[2]

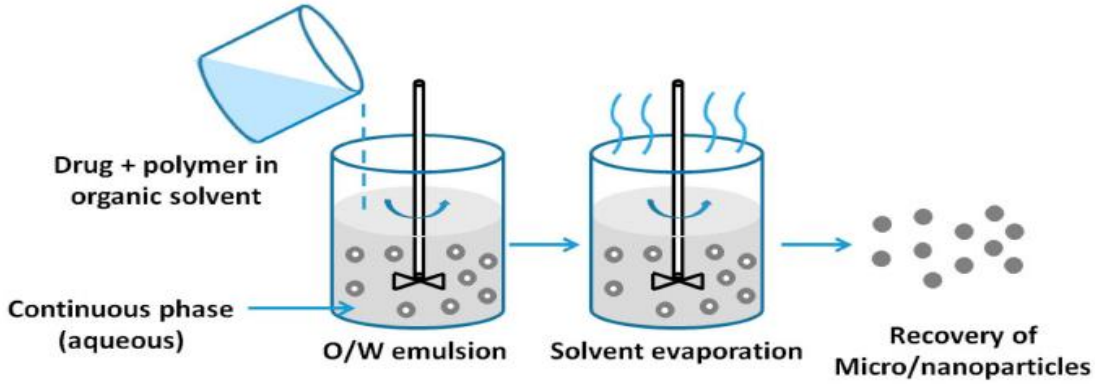

Fig No 1: - Emulsion Solvent Evaporation Method.

If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.

Emulsion- Solvent Diffusion Technique

In order to improve the residence time in colon floating micro particles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture is dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture is added drop wise to sodium lauryl sulphate (SLS) solution. The solution is stirred with propeller type agitator at room temperature at 150 rpm for 1 h. Thus the formed floating microspheres were washed and dried in a desiccator at room temperature. The following micro particles were sieved and collected.[2]

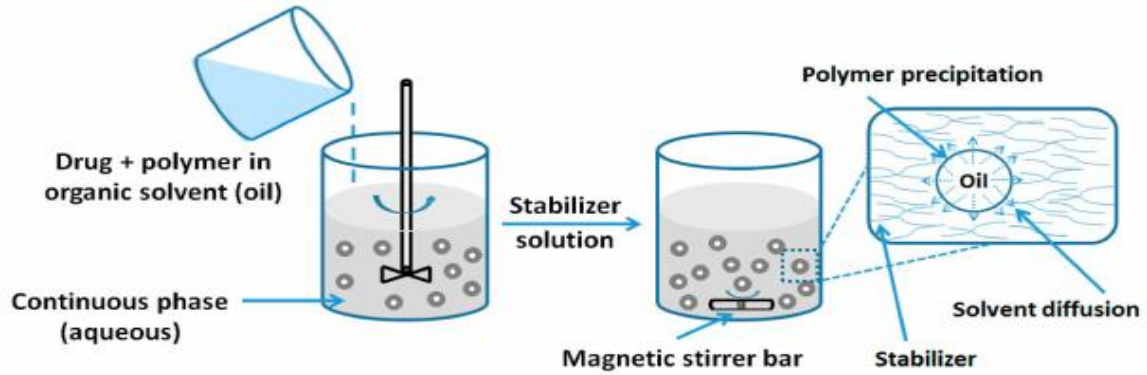

Fig No. 2: Emulsion Solvent Diffusion Technique.

Emulsion Cross linking Method

In this method drug is dissolved in aqueous gelatine solution which is previously heated for 1 h at 40°C. The solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35°C, results in w/o emulsion then further stirring is done for 10 min at 15°C. The produced microspheres are washed respectively three times with acetone and isopropyl alcohol which then air dried, dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 h cross linking and then treated with 100ml of 10 mm glycerine solution containing 0.1% w/v tween 80 at 37°C for 10 min to block unreacted glutaraldehyde.

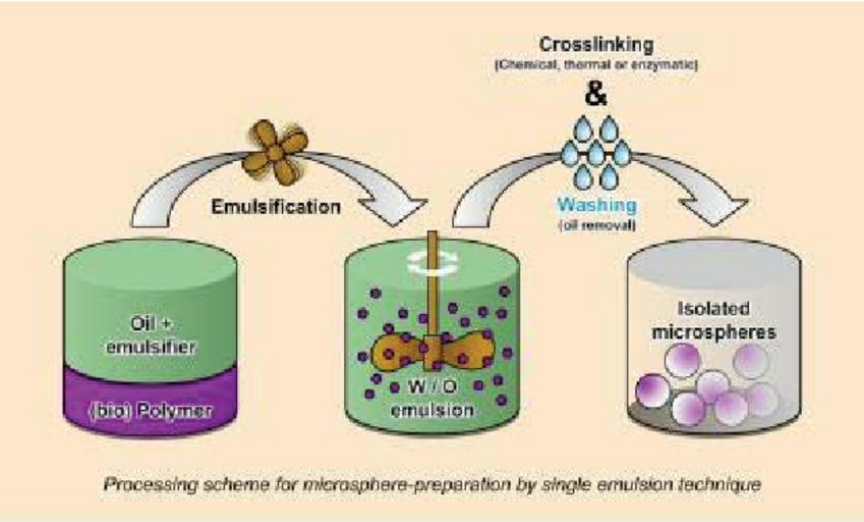

Fig No. 3: Single Emulsion Cross Linking Technique.

Multiple Emulsion Method

Multiple emulsion method involves formation of (o/w) Primary emulsion (non aqueous drug solution in polymer solution) and then addition of primary emulsion to external oily phase to form o/w/o emulsion followed by either addition of cross-linking agent (glutaraldehyde) and evaporation of organic solvent. Multiple emulsion method of preparation is ideal for incorporating poorly aqueous soluble drug, thus enhancing its bioavailability.[3,4]

Co-acervation Method

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation 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 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 polymer.

Polylactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.[5]

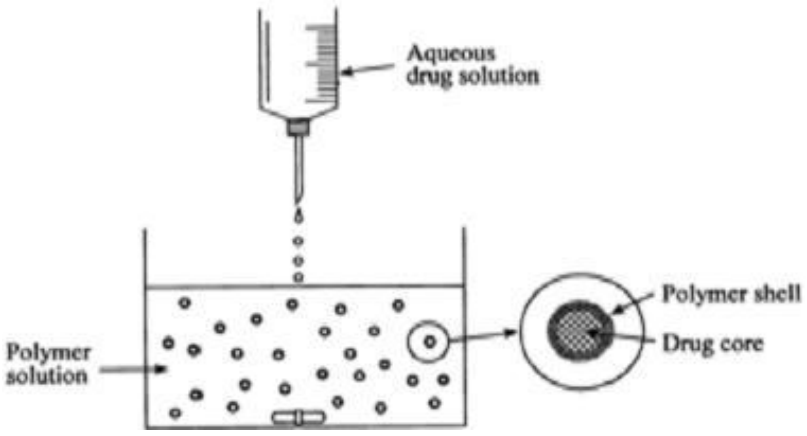

Fig No. 4: Coacervation Phase Separation.

Spray Drying Technique

In Spray drying, 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 the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100µm.

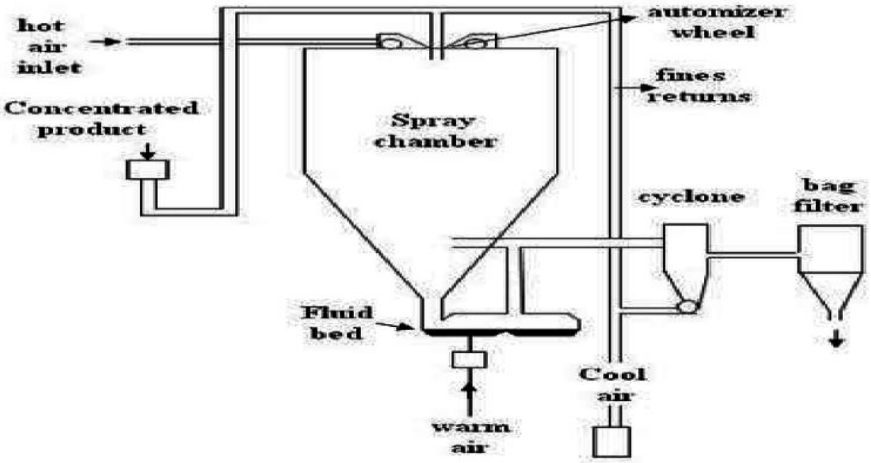

Fig No. 5: Spray Drying Process for Preparation of Microspheres.

Microparticles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and this leads to the formation of porous microparticles.

Ionic gelation method

Alginate/ chitosan particulate system for diclofenac sodium release is prepared using this technique.25% (w/v) of diclofenac sodium is added to1.2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it is added drop wise to a solution containing Ca2+/ Al 3+ chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for internal gelification followed by filtration for separation. The complete release is obtained at pH 6.4-7.4 but the drug did not release in acidic pH.[8,9]

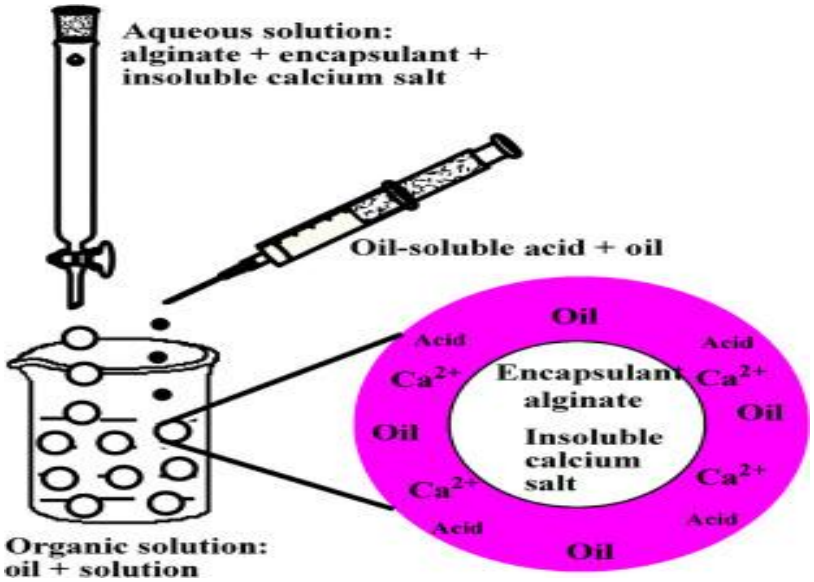

Fig No. 6: Ionic Gelation Method.

Hydroxy Appatite (HAP) Microspheres

in sphere morphology This method is used to prepare microspheres with peculiar spheres in sphere morphology microspheres were prepared by o/w emulsion followed by solvent evaporation.

At first o/w emulsion is prepared by dispersing the organic phase (Diclofenac sodium containing 5%w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase is dispersed in the form of tiny droplets which were surrounded by surfactant molecules; this prevented the droplets from co solvencing and helped them to as stay individual droplets. While stirring the DCM is slowly evaporated and the droplets solidify individually to become microsphere.

EVALUATION OF MICROSPHERES

Percentage Yield

The total amount of dried microcapsules was weighed and the percentage yield was calculated by taking into consideration the total weight of the drug and polymer used for preparation of microspheres.

Percentage Yield = Practical yield/ Theoretical yield x 100

Particle size and shape

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM).

Flow Properties of Microspheres

Flow properties of microspheres were investigated by determining by following standard procedures. All studies were carried out in triplicate.

Bulk Density

Bulk density was determined by taking a known weight of dried microspheres in a measuring cylinder and tapping 3 times from 1 inch height at 2 second interval. The bulk volume is noted and the bulk density was calculated from the following equation.

Bulk density = Weight of microspheres / Bulk volume of Microspheres

Tapped Density

Tapped density is the ratio of mass of microspheres to the volume occupied by the same mass of the powder after a standard tapping of a measure. Weighed quantity of microspheres was taken in a cylinder and tapping 300 times from 1 inch at 2 second interval.

The tapped volume is noted and the tapped density was calculated from the following equation.

Tapped density = Weight of microspheres / Tapped volume

Hausner's Ratio

Hausner's ratio is used for predicting the flow characteristics. Hausner's ratio is determined from the following formula.

Hausner's ratio = Bulk density / Tapped density

Compressibility Index

Compressibility index was determined by using bulk density and tapped density.

Compressibility index (%) = Tapped density – Bulk density / Tapped density × 100

Angle of Repose

A funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the plane. Microspheres were placed in funnel and allowed to flow freely and the height and radius of the heap of microspheres was measured.

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

Where, 'h' is the height of heap and 'r' is the radius of heap of microspheres.

APPLICATIONS OF MICROSPHERES

1. Vaccine Delivery

An ideal vaccine must fulfil the requirement of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

1. Improved antigenicity by adjuvant action

2. Modulation of antigen release
3. Stabilization of antigen

2. Targeting using microparticulate 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 relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system.

3. Monoclonal antibodies mediated microspheres

Targeting Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. Monoclonal antibody can be directly attached to the microspheres by means of covalent coupling. The Monoclonal antibody can be attached to microspheres by any of the following methods.

1. Nonspecific adsorption and Specific adsorption
2. Direct coupling
3. Coupling via reagents
4. Chemoembolization

Chemoembolization is an endovascular therapy, which involves the selective arterial embolization of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent.

5. Imaging

The particle size range of microspheres is an important factor in determining the imaging of particular sites using radio labbled microspheres. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This

phenomenon is exploited for the scintigraphy imaging of the tumour masses in lungs using labbled human serum albumin microspheres.[9]

6. Topical porous microspheres

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300µm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system.

7. Radioactive microsphere

These can be used for radio embolization of liver and spleen tumours.

Radioactive microspheres used for radio synovectomy of arthritis joint, local radiotherapy, interactivity treatment.

By imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deep vein thrombosis can be done.

CONCLUSION

This review article describes that microsphere are better choice of drug delivery system than different types of drug delivery system. In future microspheres will find the central and significant place in novel drug delivery by combining various other strategies, particularly in diseased cell sorting, increase the bioavailability of poorly water-soluble drugs, diagnostics, gene & genetic materials, safe, targeted, specific and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.[10,11]

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