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Review Article

Biodegradable Polymeric Microspheres as Drug Carriers; A Review

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ABSTRACT

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 200 µm. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy 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. One such approach is using microspheres as carriers for drugs. 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 without untoward effects. This article aims to provide a comprehensive review of advantages, methods of preparation, mechanism, routs of administration, different types of microspheres based on natural and synthetic biodegradable polymers and application of biodegradable polymeric microspheres.

INTRODUCTION

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects.

There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One of such approach is using microspheres as carriers for drugs. Microspheres are solid, approximately spherical particles ranging 1- 1000 µm in size. They are made up of polymeric substances, in which the drug is dispersed throughout the microsphere matrix. [1]

The reason behind the development of controlled drug delivery systems is to make a therapeutic agents do its best when administered into the body.

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This means a high therapeutic efficacy with minimal toxicity successful application of many therapeutic agents are hampered by a multitude of problems. Drugs administered normally distribute throughout the body interacting not only with the target cells but also with the normal healthy cells which often results in toxic effects. Conventional therapy requires frequent administration of the therapeutic agent to the patient which reduces patient compliance. Systemic administration of the drug often requires high concentrations to maintain a therapeutic effect because of the dilution effect and the difficulty of drug placement in the target site. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount for the right period of time thereby causing little toxicity and minimal side effects. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. [2]

A thorough understanding of the drug carrier, the drug and the target site is necessary for designing a controlled drug delivery system. Choice of the method for achieving controlled release in a particular application depends on the physic-chemical properties of the carrier system, potency and properties of the drug and the

location and access to the target site. Drug release from a carrier matrix is governed by the interaction of the drug with the carrier matrix. For example, the free aldehyde in glutaraldehyde cross-linked microspheres react with certain drugs. Methitrexate reacts with glutarladehyde while adriamycin does not even though both contain an amino group. Accessibility of functional group may also exert an influence. Since the physico-chemical properties of each drug is often different, the release profiles of different drugs can be different from a given matrix. It therefore become necessary to evaluate on detail the behavior of each in terms of its interaction with the matrix and the release profile. [3]

There are various approaches in delivering a therapeutic substance to the target site in a sustained or controlled release fashion. One such approach of using polymeric microspheres as carriers for drugs. Microspheres for biodegradable and non-biodegradable polymers have been investigated for sustained release depending on the final application. In the case of non-biodegradable drug carriers, when administered parentally, the carrier remaining in the body after the drug is completely released poses the possibility of carrier toxicity over a long period of time. Biodegradable carriers which degradable the body to non-toxic degradation products do not pose the problem of carrier toxicity and are more suited for parenteral application. Thus, emphasis in this review is on the approach of using biodegradable polymeric microspheres for achieving sustained release. [4]

MICROSPHERES AS DRUG CARRIERS

Microsphere based drug delivery have received considerable attention in recent years. The most important characteristic of microspheres of the microphase separation morphology which endows it with a controllable variability in degradation rate and also drug release.

Microspheres based on biodegradable polymers

Biodegradable microspheres can be prepared from certain synthetic as well as natural polymers. An important requirement of such polymers is that the degradation products should be non-toxic because such products eventually enter circulation or result in tissue deposition. Long term toxicological evolution of the degradation products therefore is important in determining the clinical suitability of such carriers. Biodegradability carrier matrices can be designed to deliver the therapeutic agent for periods ranging from a few days to a few years. [5]

Natural polymer such as proteins and polysaccharides undergo enzymatic degradation in the body. Most synthetic biodegradable polymers contain hydrolysable linkages like amide, esters, ureas and urethanes. Polypeptides undergo enzymatic degradation while synthetic polyesters such as poly(lactic acid) and poly(glycolic acid) degrade by simple hydrolysis. Enzymes area also reported to exert influence on the degradation of synthetic polyesters. [6]

Homogeneous degradation or bulk degradation involves the cleavage of the bonds at a uniform rate throughout the matrix. Degradation in this case is independent of the surface area in heterogeneous or surface degradation, the rate of degradation is constant with time.[7,8]

Preparation of microspheres

The preparation of microspheres should satisfy certain criteria. They are:

(i) The ability to incorporate reasonably concentrations of the drug,
(ii) Stability of the preparation after synthesis with a clinically acceptable shelf-life,
(iii) Controllable particle size and dispensability in aqueous vehicles for injection,
(iv) Release of active agent with good control over a wide time scale,
(v) Biocompatibility with a controllable biodegradability, and
(vi) Susceptibility to chemical modification.

The preparation of microspheres from natural polymers involves three steps.

First the solution of the polymer is disperse n a continuous medium such as vegetable oil or an organic solvent using a suitable agent. Dispersion is accomplished stirring or by ultrasonication or by high speed homogenization depending on the particle size required. The second step involves the hardening of the polymer droplets either by heat denaturation (in the case of proteins) or by chemical cross-linking using suitable cross-linking agent. The third step involves separation of the solid microspheres formed, purification and drying.[9]

Chemical cross-linking of protein microspheres can be achieved using cross-linking agents such

as formaldehyde, glutaraldehyde or by using diacid chlorides such a terephthalate chloride the method is also limited to drugs that do not have any chemical interaction with the cross-linking agent. for example glutaraldehyde interacts with salbutamol and methotrexate and formaldehyde interacts with eponephine.

Microspheres of synthetic polymers could be prepared either by the polymerization of the monomer using the techniques of suspension or dispersion polymerization or from the polymer using a suitable solvent evaporation technique. [10]

Various methods are employed for the preparation of the microspheres from polymers. Solvent evaporation is the most widely used technique. The polymer is dissolved in a suitable volatile solvent and dispersed in a continuous medium using a suitable stabilizing agent. Controlled evaporation of the solvent results in the formation of solid microspheres.

Phase separation and spray drying are some other methods used for the preparation of microspheres. In phase separation, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes the first polymer to phase separate and engulf the drug particles. Addition of a non-solvent result in the solidification of the polymer. Poly (lactic acid) microspheres have prepared by this method by using polybutadiene as the incompatible polymer. Poly (lactic acid) microspheres have temperature of 37-50^{o}C, the solvent evaporation form in solid microspheres bearing porous net work and narrow size distribution. Polymers with low melting point can be fabricated into microspheres by the hot melt technique. The molten polymer is dispersed in suitable dispersion medium and slowly cooled to form the microspheres. The method has been particularly successful in the case of polymerhyride which are susceptible to hydrolysis in the presence of moisture. [11]

Method of drug incorporation

Drugs are incorporated into the microspheres either during their synthesis or after the microspheres are formed. High loading can be achieved by in situ loading if the drug is insoluble in the dispersion medium employed for microsphere stabilization. Washing the microspheres after their preparation to remove surfactants, oils, other impurities etc., using solvents in which the drug solubility is high may result in poor loading efficiency. *In situ* loading can not be employed for drugs which are affected by temperature of microsphere preparation, solvents employed, cross-linked agents etc. if the drug is heat sensitive, the resulting drug-loaded microspheres can not be sterilized by heat. Loading into preformed microspheres incorporated. The microsphere is swollen in a suitable solvent containing high concentration of the drug. The drug molecules diffuse into the matrix which is then dried to obtain drug-loaded microspheres. The method is best suited for cross-linked microspheres which do not dissolve but only swell when equilibrated in a suitable solvent. A high payload of water soluble drugs can be obtained if the microspheres are hydrophilic and swells to a high degree in aqueous solution. The method allows the most native form of the drug to be incorporated into the matrix. [12]

Drug-polymer binding

The binding force that holds the drug to the microsphere matrix can be physical or chemical. In addition to this, hydrophobic and electrostatic interaction may also exist. Depending on the force of attachment, drug release from the matrix also varies. The drug release is expected to be faster if only physical entrapment is achieved. Drug release in such cases is modulated by a diffusion controlled mechanism.

Slow release can be achieved by chemically binding the drug to the microsphere matrix. The polymer matrix should have reactive functionalities to which the drug can be bound through a functionality available on the drug. [13]

Drugs can be either attached onto the preformed microsphere or a polymer-drug conjugate prepared by attaching the drug to the polymer chain can be further into the microsphere form. The linkage should be susceptible to degradation in the physiological environment so that the drug is released from the microsphere matrix. High loading is possible if sufficient functionalities to which drug can be bound exist on the polymer matrix. The drug release in this case will depend on the rate of cleavage of the bond linking the drug to the matrix. [14]

Route of administration

Microspheres can be used for the delivery of drugs via different routes. Route of administration is selected depending on the drug properties, disease state being treated and the

age and condition of the patient. Desirable properties of the microspheres to be used for the delivery will also change depending on the route of administration.

(a) Oral delivery

Oral delivery is the simplest way of drug administration. In oral drug delivery, the microspheres have to pass through frequently changing environment in the GI tract. There is also patient to patient variation in GI content, stomach emptying time and peristaltic activity. Although constants of the oral route are numerous, on the whole, it offers less potential danger than the parenteral route. The relatively brief transit time of about 12 h through the GI tract limits the duration of action that can be expected via the oral route.

Bioavailability of drugs with limited solubility in the stomach or intestine and small absorption rate constant can be increased by increasing the retention time in the stomach. [15]

(b) Parenteral Delivery

Most of the microsphere base controlled delivery systems are developed with the aim of using them for parenteral administration. Drug is completely absorbed in this case. Microspheres used for parenteral delivery should be sterile and should be dispersible in a suitable vehicle for injection. Hydrophilic microspheres have the potential advantage of aqueous dispersibility as opposed to hydrophobic microspheres for reconstituting them for injection. Surfactants in small concentrations are often necessary for reconstituting hydrophobic particles for injection in aqueous vehicle which are reported to cause adverse tissue reaction and affect the release of the incorporated drug. [16]

Fate of microspheres in the body

Knowledge of the fate of microspheres after parenteral administration is very important in designing a drug delivery system. The biological fate of the administered particles has been studied by radiolabelled techniques. ^{14}C, ^{131}I, ^{125}I and ^{9}Tc have been used for labeling.

Another method for the estimation of microspheres administered into the body is by using magnetite. Magnetite eatimation has the advantage that it can be easily incorporated into the microsphere matrix by physical entrapment without altering the chemical nature of the matrix. The recovery of the microspheres from the target organs can be achieved with the aid of an atomic absorption spectrophotometer.

MECHANISM OF DRUG RELEASE

Theoretically, the release of drugs from biodegradable microspheres can be classified broadly into four different categories. But in actual practice, the mechanism is more complex and an interplay of different mechanisms may operate. [17]

Degradation controlled monolithic system

In degradation controlled monolithic microsphere systems, the drug is dissolved in the matrix and is distributed uniformly throughout. The drug is strongly to the matrix and is released only on degradation of the matrix. The diffusion of the drug is slow compared with the degradation of the matrix. When degradation is by homogeneous bulk mechanism, drug release is slow initially and increases rapidly when rapid bulk degradation starts. Drug release from such type of devices is independent of the geometry of the device.

Release from a sphere is governed by the equation, where M_t is the amount of the agent released at time t, M_∞ is the amount at time t_∞ is the time for total erosion. Progesterone release from poly (glycolic-co-lactic acid) polymer films containing 10 weight% steroids is an example of this type of release.

$$M_t / M_\infty = 1-[(1-t/ t_\infty)]^3$$

Diffusion controlled monolithic system

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Degeneration of the polymer matrix affects the rate of release and has to be taken into account. Rate of release also depends on whether the polymer degrades by homogeneous or heterogeneous mechanism.

Diffusion controlled reservoir systems

Here the active agent is encapsulated by a rare controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix. Polymer that remains as such till the complete, release of drug and then degrades by homogenous mechanism so that the device is removed from the body is better for this type of delivery.

Erodible poly-agent system

In this case the active agent is chemically attached to the matrix and the rate of biodegradation of the matrix is slow compared to the rate of hydrolysis of drug polymer bond. Assuming that the rate of diffusion of the active agent from the matrix to the surrounding is rapid, the limiting step is the rate of cleavage of the bond attaching drug to the polymer matrix. [18]

TARGETING OF MICROSPHERES

Targeting is achieved by exploiting the natural pattern of a drug carrier called passive targeting i.e. by changing the natural pattern of the carrier by some means thereby directing the drug to the specific organ or tissue. This is called active targeting.

Passive Targeting

Particles administered into the body intravenously will distribute itself in different organs depending on the size of the particles. The administered particles pass through the heart with little or no uptake to the lungs where particles > 7 μm get entrapped in the capillary beds. Particles < 7μm enter into the systemic circulation. [19]

Active targeting

Active targeting includes coating the microspheres with hydrophilic cating agents which suppresses opsonization . With colloidal particles are administered into the blood streams, they may be coated with proteins such as albumin, globulin etc., depending on the nature of the material, surface charge and hydrophilicity of the particles. This is called opsonization. By coating the particles with certain polymers like poloxamer, opzonization and removal of particles by macrophages can be reduced. It is thus possible to direct particles within the body to sites such as the lung, the liver, the bone marrow or to retain them for longer periods within the systemic circulation. [20]

Targeting using magnetic microspheres

Another approach in this area is by using magnetic microspheres. In this method magnetic loaded microspheres is infused into an artery supplying a given target site. A magnet is placed externally over the target area which restricts the microsphere to that area. [21]

Intracellular targeting

Certain cytotoxic drugs are active intracellularly, but are normally discarded due to their poor intracellular influx. Intracellular pathogens are usually protected from the immune system and the chemotherapeutic agents. The poor efficacy of many therapeutic substances for intracellular bacterial and parasitic therapy is well knowm. Commonly phagocytic cells are the sites of intracellular infection. Intracellular delivery of drugs by suitable means can obviate these problems. [22]

Albumin microspheres were avidly taken up by macrophages. They have also observed that biologically active streptomycin was released from albumin microspheres inside the phagocytic cells after ingestion and intracellular degradation of microspheres.

MICROSPHERES BASED ON NATURAL POLYMERS

Protein and polysaccharides have been extensively investigated for targeted drug delivery. Natural polymers have the advantage that they pose less toxicity problems of their own. Majority of the natural polymers are susceptible to biodegradation and are generally biocompatible. A major problem with biopolymers is the presence of antigenic determinants in them. Biopolymers also differ in their molecular weight and their physical and chemical properties to varying extents depending on the source and method of isolation and purification.

Albumin microspheres

Proteins have attained considerable attention as drug carriers because of the selective uptake in tumor cells coupled with known liposomal active of many cells which is necessary for the breakdown of the polymer-drug complex. Moreover, the large m=number of functional groups present in proteins offer sites for attachment of the drug. Proteins can be combined with selection of drugs to generate derivatives whose properties are often significantly different from the free drug.

Albumin microspheres received considerable attention because of their specific organ targeting property, biocompatibility and non-antigenicity in the cross-linked or heat denatured form. The preparation procedure involves dispersion of the aqueous albumin solution in a suitable medium, solidification of

the dispersed phase and separation of the micro-particles formed.

Drug release from albumin microspheres can be controlled by changing their cross-linking density and the drug albumin ratio. But high cross-linking retards the rate of degradation. Drug to albumin ratio has its limiting factors such as solubility of the drug in albumin solution and the burst effect that occurs at high drug payloads. This can be chemically attaching the drug to the protein. Since there are many functionalities in the protein to which the drug can be anchored, high payloads can he obtained by chemically binding the drug to the matrix.

Albumin binds many drugs strongly and this binding would drug retard drug release from an injection site until the microspheres are degraded by proteolytic enzymes. Albumin microspheres of suitable size have been found to be useful for localized drug delivery. Albumin microspheres have also been investigated for oral drug delivery. Retention of the microsperes in the stomach can be improved by mixing microspheres with a bioadhesive polymer. [23]

Casein microspheres

Serum albumin microspheres are prepared from albumin separated from outdated human blood. With the prevalence of AIDS, the risk of viral contamination in blood used for the preparation of albumin is a possibility. Recently there has been considerable interest in the milk protein casein as a carrier for drugs.

The biodegradation rate of albumin and casein microspheres by radiolabelled techniques and found that casein system degraded slowly compared to albumin. [24]

Gelatin microspheres

It is nontoxic, biocompatible and biodegradable. First order release was obtained for gelatin microspheres while zero order release was obtained from ethyl cellulose coated microspheres. Gelatin nanoparticles are reported to be taken up by some tumour cells which do not take albumin nanoparticles. [25]

Polysaccharide microspheres

Biocompatibility and biodegradability of many naturally occurring polysaccharides make them useful as drug carriers. Chitin, starch, dextran etc., are some polysaccharides used in drug delivery applications. Many investigations have been reported on the use of chitin, chitosan and their derivatives as drug carriers for targeted, controlled or sustained delivery of drugs . It has been demonstrated that partially deacetylated chitin is a substrate for lysozyne.

Partially deacetylated chitin and its glutaraldehyde cross-linked hydrogels are degraded by lysozyme but the degradation rate is reported to be rather slow. There are many reports on the use of chitosan as a drug carrier for oral and parenteral formulations. The release of drugs from the microsphere matrix was a function of the cross-linking density of the microspheres, drug payload, particle size and aqueous solubility of the drug. Chitosan microspheres prepared by the glutaraldehyde cross-linking of an aqueous acetic acid dispersion of chitosan have loaded with proteins such as bovine serum albumin (BSA) and the release was examined in vitro.

Implantation of the placebo chitosan microspheres in the gluteal muscle of rats has shown that the glutaraldehyde cross-linked microspheres were well tolerated by the tissue and were not degraded completely even after six months. The degradation appeared to be mostly due to surface erosion. These studies have demonstrated the potential of cross-linked chitosan microspheres as a potential drug carrier for the prolonged delivery of drugs and macromolecules such as polypeptides.

Starch microspheres have also have been investigated for drug delivery. Starch is one of the most abundant biopolymers consisting of glucopyranose units and hydrolyzes completely to yield D-glucose. Because of the presence of free OH groups in starch, it is susceptible to derivatization with a number of reagents. Due to their biocompatibility and biodegradability, starch microspheres of size 15-80 μm diameter were used for the temporary embolization to improve regional drug delivery.

Dextran also attracted attention as a drug carrier because of it biocompatibility and biodegradability. The polymer is also susceptible to chemical transformations using a variety of regents. Carboxylated or sulphonated polymer can be prepared by carboxymethylation or sulphopropylation. This acts as cation exchange drug carrier. Anionic group of carboxylated or sulphonated dextran interacts with basic group of drug such as adriamycin to form ionic salt complex. This salt exchange the free drug for other cations. [26]

MICROSPHERES OF SYNTHETIC BIODEGRADABLE POLYMERS

Synthetic polymers have the advantage that can be easily and reproducibly prepared. They can be copolymerized with one another to alter their physical, chemical and mechanical properties and can be prepared as low or high molecular weight materials by suitable reaction conditions. Chemical bonds which are susceptible to degradation include amides, esters, ortho esters, acetals, glycosides and related groups. Biodegradability of the polymer depends on many factors such as polymer structure, molecular weight, the physical form of the implanted material and the environment in which the polymer is placed. Since many proteolytic enzymes specifically catalyse the hydrolysis of peptide linkage adjacent to substituents in proteins, substituted polymers containing benzyl, hydroxyl, carboxymethyl and phenyl groups have been prepared to improve biodegradability.

Polyester microspheres

Aliphatic polyesters have been extensively investigated as drug carriers. Degradation mechanism for all polyesters appears to e due to homogeneous erosion by random hydrolytic chain scission. Poly (lactic acid), poly(glycolic acid) and their copolymers have been extensively studied as drug carriers. The most important property of these polymers which makes them attractive as degradable drug carriers is that they form endogenous metabolites lactic and glycolic acids on biodegradation. Effect of enzymes on the biodegradation of these polymers is a subject of controversy. They possess excellent tissue compatibility. The polymers have prepared in microspherical form for use as drug carriers by the solvent evaporation techniques. Methylene chloride is the solvent usually employed for dissolving the polymer. If the drug incorporated is insoluble in the solvent used for dissolving the polymer, drug is distributed as discrete particles through the microsphere. If the drug is completely soluble, it could crystallize as the solvent evaporates to give discrete drug-rich domains scattered throughout the microsphere matrix or should remain molecularly dispersed in the matrix and not crystallize. Low temperature phase separation has been another method used for the preparation of polylactide microspheres. Drugs particles are dispersed in the polymer solution and a non-solvent is added to desolvate the polymer and the microspheres formed are separated. The lactide and glycolide polymer induce minimal inflammatory response when introduced into the body. The degradation products are removed by body constituents. The rate of degradation of copolymers depend on the ratio of poly(Lactic acid) to poly(glycolic acid) in the copolymer. The polymers in their microspherical form have been studied as carriers for the prolonged delivery of a number of drugs and as an embolization agent. [27]

Polyanhydride microspheres

Polyanhydrides have received increasing attention in recent years because they are biocompatible and non toxic. the easily hydrolysable linkage makes it possible to prepare anhydrides with wide range of degradation rates by changing the chemical structure of the back bone. Highly hydrophobic polyanhydrides degrade by surface erosion. Degradation rate was found to change with the length of the alkyl group in the polymer backbone degradation rate can also be varied by copolymerizing with sebacic acid. By changing the composition of the copolymer a wide range of degradation rate can be obtained. But the presence of hydrophilic matrix causes the release of drug by diffusion and a good correlation between drug release and polymer degradation is not obtained. Because the anhydride bond is highly sensitive to water, normal method of microsphere preparation like solvent evaporation cannot be used which requires an aqueous phase. Microspheres are made from polyanhydrides by interfacial condensation and by hot melt technique. Microspheres made by polycondensation method were found to e irregular in shape and had a rough surface. Release was found to be fast and polymer degradation always lagged behind the drug release. [28]

Methods of Preparation

Preparation of microspheres should satisfy certain criteria:

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

Methods use of preparation of microspheres

1. Solvent evaporation method,
   a) Single emulsion technique.
   b) Double emulsion technique.
2. Coacervation phase separation method.
3. Spray drying and spray congealing method.
4. Polymerization method.

General methods of preparation

Choice of the technique mainly depends on the nature of the polymer used, the drug, he intended use & the duration of therapy. These include in situ polymerization, solvent evaporation, coacervation-phase separation, spray drying & spray congealing, etc.

1. Solvent Evaporation Method

a) Single emulsion technique:

The microparticulate carriers of natural polymers, i.e. those of proteins & carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved/ dispersed in aqueous medium followed by dispersion in the non aqueous medium. Ex: oil. In the 2nd step, cross linking of the dispersed globule is carried out either by means of heat or by using chemical cross linkers. The chemical cross linking agents used –gluteraldehyde, formaldehyde, terephthalate chloride, diacidchloride, etc.

Crosslinking by heat is effected by adding the dispersion to previously heated oil. Heat denaturation is not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation. [29](Fig.1)

b) Double emulsion technique

Involves the formation of the multiple emulsions or the double emulsion of type w/o/w & is best suited to the water soluble drugs, peptides, proteins & the vaccines.

The aqueous protein solution is dispersed in a lipophilic organic continuous phase which is generally consisted of polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization before addition to aqueous solution of PVA .this results in formation of double emulsion which is then subjected to solvent removal by solvent evaporation maintaining the emulsion at reduced pressure or by stirring so that organic phase evaporates out. [30](Fig.2)

Examples: hydrophilic drugs like LHRH agonist, vaccines and proteins.

2. Coacervation phase separation method

Specially designed for preparing the reservoir type of the system, i.e., to encapsulate water soluble drugs e.g. peptides, proteins, matrix type particularly, when the drug is hydrophobic in nature e.g., steroids. In matrix type device, the drug or the protein is soluble in the polymer phase. The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called the coacervates. The coacervation can be brought about by addition of the third component to the system which results in the formation of the two phases, one i.e. supernatant, depleted of the polymer.

In this technique, the polymer is first dissolved in a suitable solvent & then drug is dispersed by making its aqueous solution, if hydrophilic or dissolved in t he polymer solution itself, if hydrophobic. Phase separation is then accomplished by changing the solution conditions. [31] (Fig.3)

3. Spray drying and spray congealing:

These 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 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 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 1-100 μm. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles. [32](Fig.4)

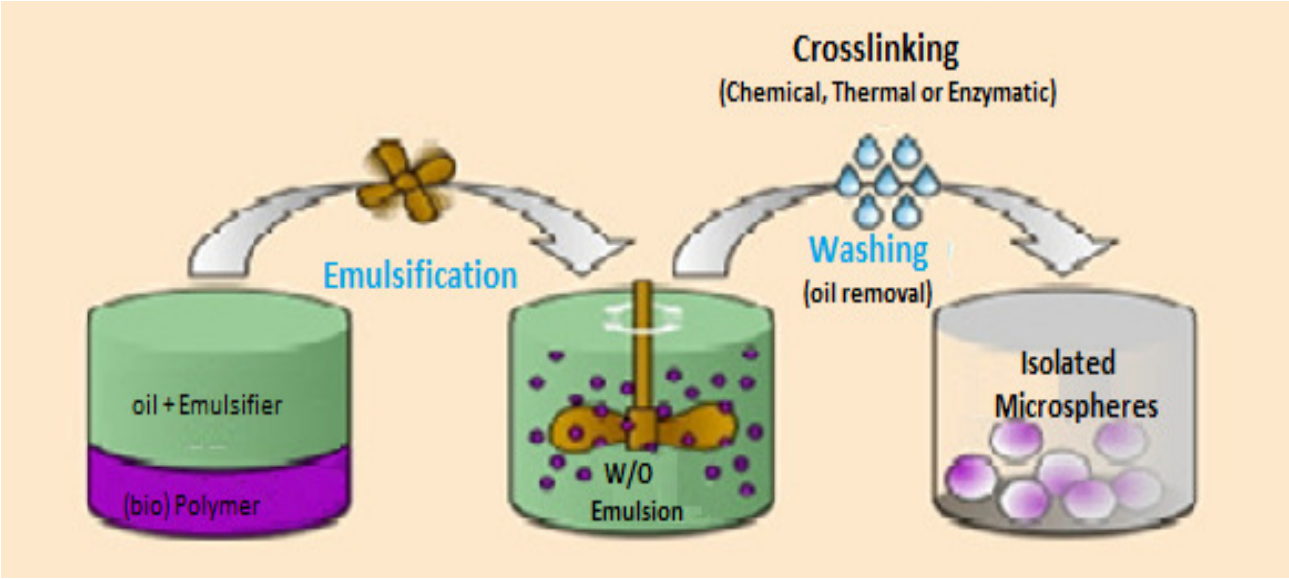

Figure 1: Processing scheme for microspheres-preparation by single emulsion technique

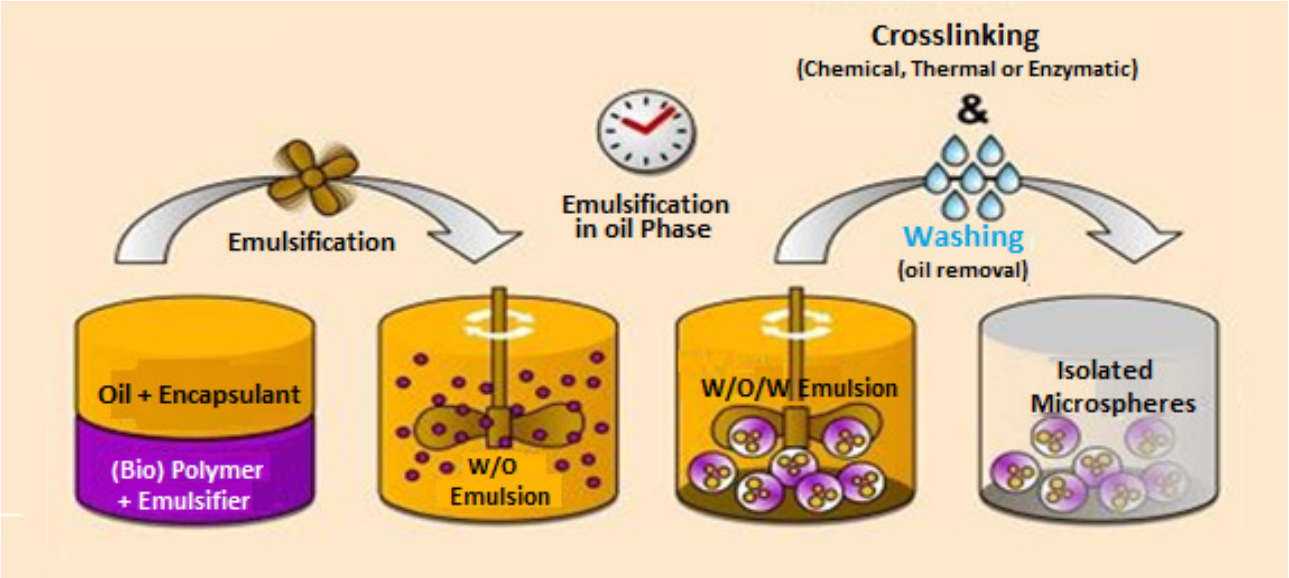

Figure 2: Processing scheme for microspheres-preparation by double emulsion technique

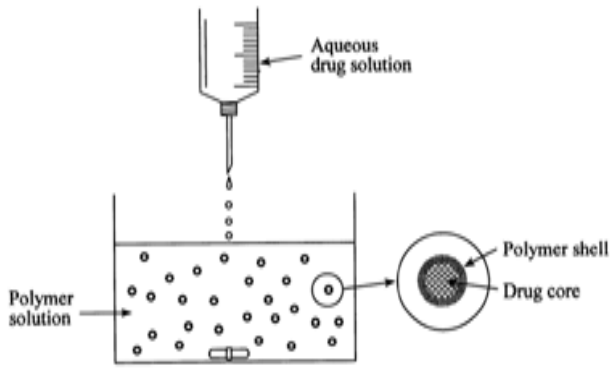

Figure 3: Coacervation phase separation method

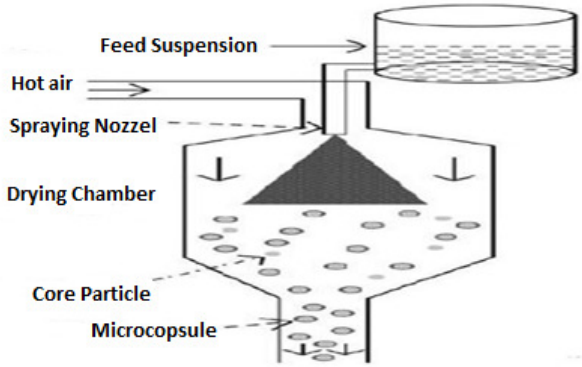

Figure 4: Spray drying and spray congealing

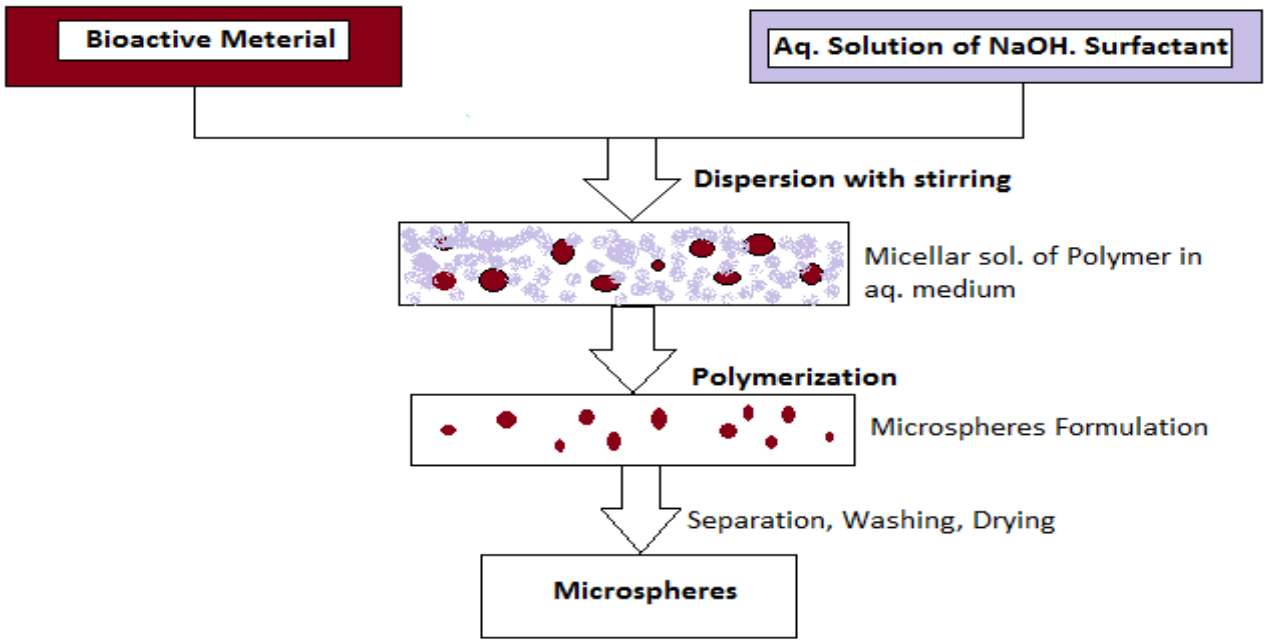

Figure 5: Polymerization method

4. Polymerization method

I. Normal polymerization
II. Interfacial polymerization.

NORMAL POLYMERIZATION

Proceeds using techniques like bulk, suspension precipitation, emulsion & micellar polymerization processes. In bulk polymerization, a monomer along with initiator is heated to initiate polymerization. Initiator is added to accelerate the rate of reaction. Drug is added during process of polymerization. The polymer so obtained is fragmented to microspheres.

ADVANTAGE - Formation of the pure polymer,
DISADVANTAGE - Very difficult to dissipate the heat of reaction, which can adversely effect the thermolabile active ingredients. [33]

SUSPENSION POLYMERIZATION

Suspension polymerization is also called as bead/pearl polymerization. Carried out by heating the monomer or mixture of monomers with active principles(drug) as droplets dispersion in a continuous phase. The droplets may also contain an initiator & other additives.
The emulsion polymerization, differs from the suspension polymerization as due to presence of initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules.
The suspension & emulsion polymerization can be carried out at lower temperature, since continuous external phase is normally water through which heat can easily dissipate. The 2 processes also lead to the formation of higher mol. wt polymer at relatively faster rate.
Major disadvantage of suspension & emulsion polymerization - association of polymer with the unreacted monomer & other additives. [34]

INTERFACIAL POLYMERIZATION:

Involves reaction of various monomers at the interface between the 2 immiscible liquid phases to form a film of polymer that essentially envelopes the dispersed phase. In this 2 reacting monomers are employed one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. Monomer present in either phases diffuse rapidly 7 polymerize rapidly at the interface. If the polymer is soluble in the droplet it will lead to the formation of monolithic type of the carrier on the other hand if polymer is insoluble in the monomer droplet, the formed carrier is of capsular(reservoir) type. The degree of polymerization can be controlled by the reactivity of monomer chosen, their concentration, the composition of the vehicle of either phases & by the temperature of the system. The particle size can be controlled by controlling the droplets or globule size of the disperse phase. The polymerization reaction can be controlled by maintaining the concentration of the monomers, which can be achieved by the addition of an excess of the continuous phase. [35](Fig.5)

Drug loading and drug release kinetics

The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc. Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or micro-morphology of the carrier and the properties of the polymer itself.

The drugs could be released through the microspheres by any of the three methods, first is the osmotically driven burst mechanism, second by pore diffusion mechanism, and third by erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuse into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst effect is mainly controlled by three factors the macromolecule/polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres. The pore diffusion method is named so because as penetrating water front continue to diffuse towards the core. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix.

Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, i.e. whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients. [36,37]

Applications [38]

- Assay - Coated microspheres provide measuring tool in biology and drug research.
- Buoyancy - Hollow microspheres are used to decrease material density in plastics (glass and polymer).
- Ceramics - Used to create porous ceramics used for filters (microspheres melt out during firing, Polyethylene Microspheres)
- Cosmetics - Opaque microspheres used to hide wrinkles and give color, Clear microspheres provide "smooth ball bearing" texture during application (Polyethylene Microspheres)
- Drug Delivery - Miniature time release drug capsule (polymer).
- Electronic paper - Dual Functional microspheres used in Gyricon electronic paper .
- Personal Care - Added to Scrubs as an exfoliating agent (Polyethylene Microspheres).
- Spacers - Used in LCD screens to provide a precision spacing between glass panels (glass).
- Standards – Monodisperse microspheres are used to calibrate particle sieves, and particle counting apparatus.
- Retroreflective - Added on top of paint used on roads and signs to increase night visibility of road stripes and signs (glass).
- Thickening Agent - Added to paints and epoxies to modify viscosity and buoyancy.

CONCLUSION

Biodegradable polymer microspheres appear to have potential applications in controlled drug delivery. Development in polymer science has made it possible to synthesize polymers with a wide range of biodegradability. Biodegradability can be tailored to the desired degree by copolymerization of two or more monomers at varying ratios, introducing cross-inking between the chains, blending one polymer with the other etc. a number of methods have been devised to prepare microspheres of desired size, shape and surface properties. The size, surface charge and surface hydrophilicity of the microspheres have been found to be important in determining the fate of particles in vivo. Attachment of antibodies to spheres loaded with therapeutic agents offers opportunity to target them to the neoplastic tissue. Passive targeting using microspheres of appropriate sizes allows localized action of the therapeutic substance in many organs of the body.

Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly. This approach may prove to be potentially useful in the treatment of macrophage as, associated diseases. The possibility of loading cytotoxic drugs, vaccines and polypeptides into preformed microspheres of proteins sand polysaccharides allow the most native form of the therapeutic substance to be incorporated into the carrier thus avoiding the adverse effects of undesirable organic solvents, cross-linking agents, pH of the medium, temperature, ultrasound etc, increasing the biological life of carrier matrices based on proteins and polysaccharides by adjusting the cross-linking density offers opportunity to extend the period of drug delivery. Recent studies in the uptake of microspheres by peyer's patches have opened up the possibility of delivering many vaccines by the oral route.

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