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Review Article

VARIABLES EFFECTING DRUG ENTRAPMENT EFFICIENCY OF MICROSPHERES: 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 microsphere can overcome such problems by enhancing the loading efficiency of a particular drug and minimizing the wastage of drug. 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. For success of microspheres as drug delivery system its necessary to obtained desired particle size, maximum drug entrapment, mucoadhesion, swelling index and drug release. This can be obtained by optimizing the formulation as well as process variables but before designing the microspheres formulation deep understanding the effect of various variables on characteristics of microspheres is necessary. The intent of the paper is to highlight the reported study on various formulation variables those are might be useful to encountered several problems which is reason for low drug entrapment efficiency

Key**words:** Novel drug delivery system, Controlled release, Microspheres, Drug entrapment.

Introduction:

Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres.[1] which modulates the release and absorption characteristics of the drug. Dosage forms that can precisely control the release rates and target drugs to a specific body site have created enormous impact on the formulation and development of novel drug delivery systems.[2] Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner.[3, 4] Microspheres constitute an important part of these particulate DDS by virtue of their small size and efficient carrier characteristics. Microspheres have many applications in medicine, with the main uses being for the encapsulation of drugs and proteins. A protein delivery system with high loading capacity is very advantageous, because it can prevent the loss of antigen and also limit the need of administering high level of carrier.[5] Several difficulties are faced in designing of microspheres better absorption and enhanced bioavailability. The formulation variables have a variety of effects on the physicochemical properties of the microspheres. The bio-distribution of the drug from microspheres is highly dependent on the size and % drug entrapment of the microspheres. Release kinetics of the microsphere matrix is depend on the various factors i.e. type of polymer used [6], concentration of polymer[7-11], drug to polymer ratio, solubility of drug, dispersed phase to continuous phase ratio etc. These variables directly affect the loading efficiency of the microspheres. Therefore, process optimization and formulation optimization are advantageous for the efficient entrapment of water-soluble labile drugs like therapeutic enzymes. Optimum formulation can be made possible by understanding of variables which affect the particle size, drug entrapment, swelling index, and drug release of microspheres. The variables increases the drug entrapment efficiency are given below:

1. High polymer conncenteration
2. Low drug to polymer ratio
3. Low stirring speed
4. Low conncenteration of emulsifier
5. High conncenteration of cross linker
6. High drug polymer interaction
7. Low solubility of drug in continous phase
8. Low solubility of polymer in organic solvent
9. High solubility of organic solvent in water

Method for preparation of Microspheres

1. Spray Drying

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 evaporate instantaneously leading the formation of the microspheres in a size range 1-100µm. Micro particles 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 micro particles.[8]

2. Spray congealing.

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 cold 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.[9]

3. Solvent Evaporation

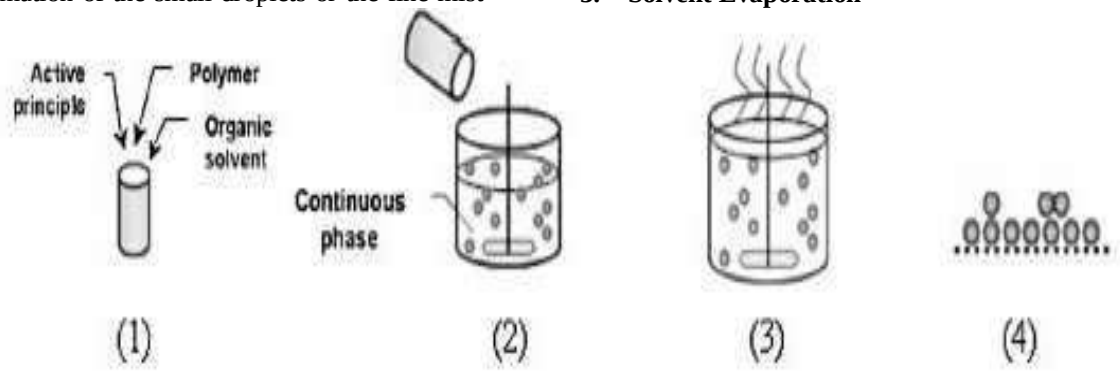

Fig-1: The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microsphere. The mixture is then heated if necessary to evaporate the solvent. The solvent Evaporation technique to produce microspheres is applicable to wide variety of core materials.[10]

4. Single emulsion technique

The microspheres can be prepared by using any of natural polymers, i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in the non aqueous medium e.g., oil. In the second step of preparation, cross linking of the dispersed globules carried out. The cross-linking agents can be achieved either by means of heat or by using cross-linking agents used include glutaraldehyde, formaldehyde, diacid chloride, etc. cross linking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is however, not suitable for the thermoliable drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation fig2.

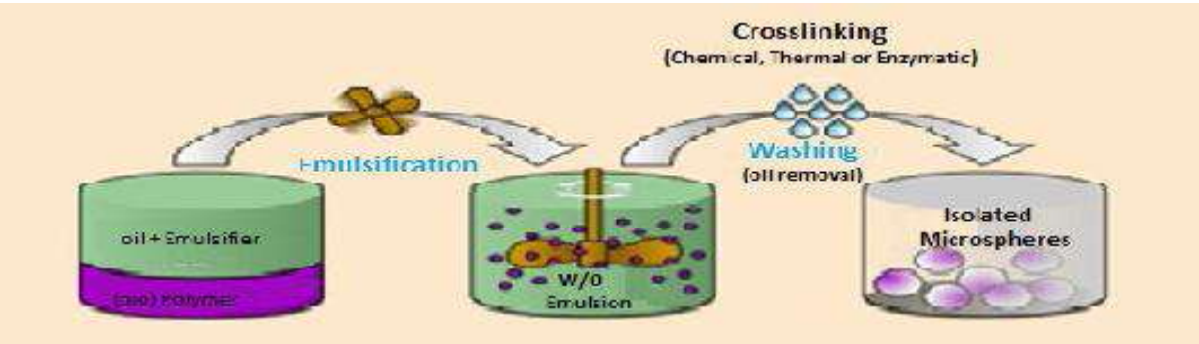

Fig-2: Single emulsion technique

5. Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. a number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction[11]

6. Polymerization techniques

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

I. Normal polymerization

II. Interfacial polymerization.

Both are carried out in liquid phase.

I. Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

II. Interfacial polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.[12]

7. Phase separation coacervation technique

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. Poly lactic 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, them 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.[13]

Factors influencing drug entrapment efficiency of microspheres:

1. Concentration of the polymer in dispersed phase:

Encapsulation efficiency increases with increasing polymer concentration For example, the encapsulation efficiency increased from 53.1 to 70.9% when concentration of the polymer increased from 20.0 to 32.5% .[14] High viscosity and fast solidification of the dispersed phase contributed to reduce porosity of the microparticles as well.[15] The contribution of a high polymer concentration to the loading efficiency can be interpreted in three ways. First, when highly concentrated, the polymer precipitates faster on the surface of the dispersed phase and prevents drug diffusion across the phase boundary.[16] Second, the high concentration increases viscosity of the solution and delays the drug diffusion within the polymer droplets.[17] Third, the high polymer concentration results large size of microspheres which result in loss of drug from surface during washing of microspheres is very less as compare to small microspheres. The encapsulation efficiency of the microspheres improved as the polymer concentration increase in oil phase and PVA concentration decreased in aqueous phase.

2. Drug: Polymer Ratio (DPR):

The drug entrapment efficiency within microspheres decreases when ratio of DPR increases. The encapsulation efficiency is significantly increasing as the DPR decreased. The encapsulation efficiency of microspheres significantly increase as the amount of polymer is increased at the same amount of drug in the dispersed. [18]

3. Interaction between drug and polymer:

Interaction between protein and polymer contributes to increasing encapsulation efficiency.[19] Generally, proteins are capable of ionic interactions and are better encapsulated within polymers that carry free carboxylic end groups than the end-capped polymers. On the other hand, if hydrophobic interaction is a dominant force between the protein and the polymer, relatively hydrophobic end-capped polymers are more advantageous in increasing encapsulation efficiency.[20] In certain cases, a co-encapsulated excipient can mediate the interaction between protein and polymer.[21] For example; encapsulation efficiency increased when gamma hydroxypropyl cyclodextrin (g-HPCD) were co-encapsulated with tetanus toxoid in PLGA microparticles. It is supposed that the g-HPCD increased the interaction by accommodating amino acid side groups of the toxoid into its cavity and simultaneously interacting with PLGA through Van-der Waals and hydrogen bonding forces.

4. Solubility of drug in continuous phase:

If the drug is more soluble in continuous phase, more drug loss in the continuous phase is occurs due to diffusion of drug from dispersed phase to continuous phase. If the solubility of the drug in the continuous phase is higher than in the dispersed phase, the drug will easily diffuse into the continuous phase during this stage which tends to decrease the encapsulation efficiency. For example, the encapsulation efficiency of quinidine sulfate was 40 times higher in the alkaline continuous phase (pH 12), in which quinidine sulfate is insoluble) than in the neutral continuous phase (pH 7), in which quinidine sulfate is very soluble. [22]

5. Effect of concentration of emulsifier:

Thakkar et al investigated the effect of emulsifier on the size, encapsulation efficiency and drug entrapment of the microspheres prepared using a natural polymer (bovine serum albumin) BSA using emulsification chemical cross-linking method. Results from this investigation shows that increase in concentration of Span-85 decrease the encapsulation efficiency of microspheres in some extent. This is due to fact that increase in Span-85 concentration leads to stabilization of small droplets and results in smaller microspheres. Loss of drug from surface of small microspheres is more as compared to larger microspheres

during washing [23]. Drug loading decreased as the concentration of DCM was increased.[24]

6. Effect of method of preparation:

The solvent evaporation method is popularly used for microsphere preparation because of its simplicity, reproducibility, and fast processing with minimum controllable process variables that can be easily implemented. But it is frequently used for water insoluble drugs, as the entrapment efficiency of water-soluble drugs is low due to drug loss from the organic emulsified polymeric phase before solidification of polymer in the microspheres.

7. Effect of Different Stirring Rates on Drug Content:

The stirring rate of emulsion system is one of the frequently studied process parameters in microspheres technology. The effect of this parameter on biopharmaceutical properties of microspheres containing drug and matrix polymer was often observed. The drug content (9-21%) increases with increasing particle size for each sample of microspheres prepared at different stirring rates. Furthermore, drug content determined for the biggest size fractions was higher than theoretical drug content in both series, although this effect was more expressed in the system without chitosan. Significance of the influence of particle size on drug content was also statistically confirmed.

8. Effect microcapsulation time:

The loading efficiencies were found to be significantly affected by the time of microencapsulation. Loading efficiency increases as the time of microcapsule formation increases. The micro encapsulation efficiency for sodium alginate–sodium CMC was found higher compared to sodium alginate–HPMC and sodium alginate–carbopol 934P. The microencapsulation efficiencies were found unaffected by the different ratios of polymer mixture.

9. Rate of solvent removal:

The method and rate of solvent removal influence the solidification rate of the dispersed phase.as well as morphology of the resulting microparticles. [25] In the emulsionsolvent evaporation/extraction method, the solvent can be removed by (i) evaporation, in which the solvent is evaporated around its boiling point or (ii) extraction into the continuous phase. The rate of solvent removal can be controlled by the temperature ramp or the evaporation temperature in the former and by the volume of the dilution medium in the latter. PLGA microparticles containing salmon calcitonin (sCT) were prepared by emulsification, followed by different solvent removal processes [26, 27]. In the temperature dependent solvent removal process, the solvent (methylene chloride) was removed by increasing the temperature from 15 to 40°C at different rates. The microparticles that resulted from this process had a hollow core and a porous wall. The core size and wall thickness were dependent on the temperature ramp. A rapid rise in temperature resulted in a thin wall and a large hollow core, whereas a stepwise temperature rise (15 to 25, then to 40°C) resulted in a reduced core size. It is believed that the hollow core was due to the rapid expansion of methylene chloride entrapped within the solidified microparticles. Even though it is generally assumed that fast polymer solidification results in high encapsulation efficiency. [28] Here, the encapsulation efficiency was not affected by the solvent evaporation temperature. It may be due to the different processing temperatures influenced not only the rate of polymer solidification but also the diffusivity of the protein and its solubility in water. While the high temperature facilitated solidification of the dispersed phase, it enhanced diffusion of the protein into the continuous phase, compromising the positive effect from the fast solidification.

10. Effect of cross linking agent concentration:.

Higher the conncenteration of cross linking agent then higher will be the entrapment efficiency. The higher amount of glutaraldehyde appears to favor the cross-linking reaction, and hence spherical free-flowing microspheres were obtained with an increase in loading efficiency.[29]

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