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Factors Affecting Microspheres Formation

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ABSTRACT

The current review provides an in-depth discussion of multiple factors influencing microspheres formation which ranging from degree of speed by homogenizers, duration of mixing, concentration of polymers, selection of aqueous and oily phase and their ratios, viscosity role, and reasons behind different sizes of spheres, texture of microspheres ie. rough or smooth, entrapment efficiency, role of emulsifier, importance of cross linking agents with their concentration, solubility ,temperature influence in formation of spheres, solvent selection criteria, drug delivery from surface of microspheres etc. forms ground work and essential to go through all above mentioned factors in order to develop of ideal and in turn to improve stability of microspheres as multi particulates and improve knowledge behind updates of production of microspheres.

Keywords: Aqueous and Oily Phase role, Emulsifier, Stirring speed, Conc. of Polymers in formation of Microspheres, PDE.

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INTRODUCTION

Microspheres were going to be one of novel technique prepared by various microencapsulation techniques, 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. In this regard it is necessary to monitor all parameters physically, chemically characteristic properties of the excipients and methods. Of all parameters few of them mentioned in short way to enhance encapsulation efficiency, total yield and stable product.

Concentration of the Polymer in Dispersed Phase

When polymer concentration was increased in the formulations, correspondence was increased to the Higuchi equation Results from different study shows that the particle size, swelling, loading efficiency and rate of drug release from the microspheres depended on the polymer concentration and the type of polymer used. Encapsulation efficiency increases with increasing polymer concentration[1,2.3], For example, the encapsulation efficiency increased from 53.1 to 70.9%. When concentration of the polymer increased from 20.0 to 32.5% High viscosity and fast solidification of the dispersed phase contributed to reduce porosity of the microparticles as well 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[4], Second, the high concentration increases viscosity of the solution and delays the drug diffusion within the polymer droplets[5] ,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. Thus size of microspheres is also affecting the loading efficiency[6]. The entrapment efficiency increases with an increase in the albumin concentration because with an increase in the albumin concentration, more viscous solutions are formed that can more efficiently prevent the dissolution of celecoxib in the external phase of the emulsion Agrawal et. al studied the effects of variables such as polymer concentration on the particle size, drug release and loading efficiency of microspheres at increasing Polymer concentrations (i.e., at drug–Polymer ratios from 1:2 to 1:6) increased from 135.3 to 163.4 mm. Size of microspheres was found to be increased with the increase in the concentration of drug. It can be attributed to the fact that with the higher diffusion rate of non-solvent to polymer solution the smaller size of microcapsules is easily obtained. This increase in particle size of the microspheres can be attributed to an increase in viscosity with increasing

polymer concentrations, which resulted in larger emulsion droplets finally in greater microsphere size. The release of drug from microspheres decreased as the polymer concentration increased, suggesting that drug release could be controlled by varying the polymer concentration. The results might also be explained by the fact that the higher polymer content resulted in larger particles with proportionately less drug, so that the drug polymer ratio was changed and thus release was reduce[7]. Another study shown that increase of mean particle size with increase in polymer concentration may have occurred due to the fact that as polymer concentration increases it produces a significant increase in the viscosity in a fixed volume of solvent, thus leading to an increase of the emulsion droplet size and finally a higher microsphere size[8-18]. The drug entrapment efficiency of microspheres was also improved with changing the concentration of drug and polymer in the internal phase to the higher concentration. This may be due to the increase in the viscosity of the internal phase that reduces the migration of the drug molecules in the aqueous phase. Results from study by Lakshmana Prabu S et. al revealed that the drug content of microspheres was not affected by the volume of dichloromethane, but the particle sizes were found to change significantly. This may also be due to the increase in the volume of dichloromethane leads to decrease in viscosity of the internal phase could be an effective factor in the droplet size of the emulsion in the aqueous medium. In this case, it seems that the shear effect of the propeller is able to break the large droplets into smaller ones, which are solidified into microspheres on solvent evaporation.

Drug Polymer Ratio (DPR)

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. Trivedi et. al prepared aceclofenac microspheres by emulsion-solvent evaporation method using Eudragit RL100, Eudragit RS100 and Eudragit S100. Results from this study clearly indicate that encapsulation efficiency is significantly increasing as the DPR decreased[19]. Drug release from microspheres is notably affected by the ratio of the drug to the polymer as increasing in the first causes faster drug release. By increasing the amount of drug loading, a point will be reached when the solid drug particles upon dissolution will begin to form continuous pores or channels within the matrix. Under these circumstances, the path of release for drug molecules will be diffusion within the channels formed from areas where drug has previously leached out from the matrix [20,21]. In other words, as the amount of drug content is increased the matrix will become more porous as drug is leached out from the polymer and thus faster drug release rate occurs in microspheres

preparation. When the drug: polymer ratio increased from 1:1 to 1:1.5 and 1:2, the yield was gradually decreased by increasing drug: polymer ratio due to increasing the drug: polymer ratio increase the viscosity of the solution in which solvent get evaporated rapidly before mixing with continuous phase so it formed as a fibers and aggregates which reduce the yield. Entrapment efficiency of the drug in microspheres was increased with increasing drug: polymer ratio because increased polymer amount provides more binding site for the drug molecules. Particle size of the microspheres was increased with increasing drug: polymer ratio. This can be explained as when the drug: polymer ratio was increased the polymer solution was more viscous which produce larger droplet when poured in to the continuous phase, so particle size was increased. *In vitro* drug release was decreased with increasing drug: polymer ratio due to increasing the diffusional path length of drug molecules.

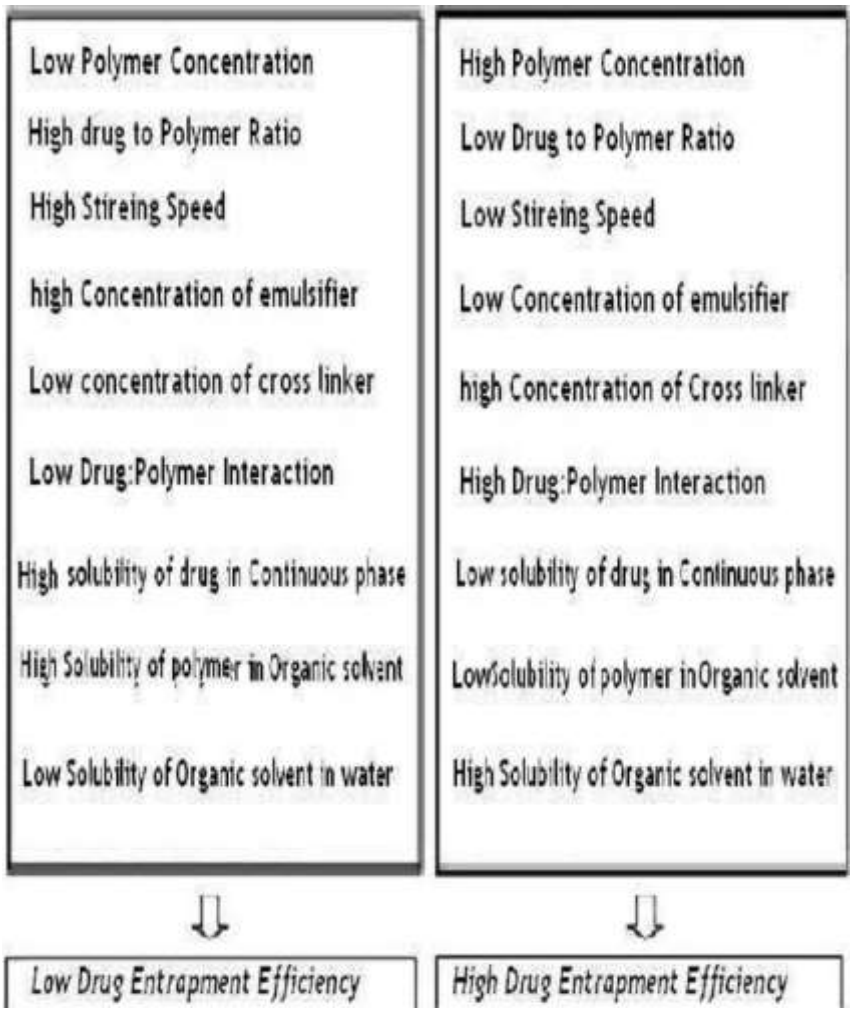
Solubility of Polymer in the Solvent

A lower molecular weight polymer had a higher solubility in methylene chloride than a higher molecular weight polymer. End-capped polymers, which were more hydrophobic than non-end-capped polymers of the same molecular weight and component ratio, were more soluble in methylene chloride. Diffusion of drugs into the continuous phase mostly occurred during the first 10 minutes of emulsification; therefore, as the time the polymer phase stayed in the non-solidified (semi-solid) state was extended, encapsulation efficiency became relatively low. In Mehta's study, polymers having relatively high solubility in methylene chloride took longer to solidify and resulted in low encapsulation efficiencies, and vice versa .Polymers having higher solubility in methylene chloride stayed longer in the semi-solid state, the dispersed phase became more concentrated before it completely solidified, resulting in denser microparticles.

Selection of Solvent System for the Dispersed Phase

With a decrease in concentration (ethanol), the surface became rough and porous. These findings suggested that these pores provided a channel for release of drug from the microspheres. The use of increasing volumes of ethanol produced microspheres with increasing drug release. According to bulk density experiments, the smallest value was obtained from the microspheres prepared with 3 mL of ethanol. It was seen that as the particle size increased, the bulk density decreased. That was because, the bulk density decreased due to the increase in the particle size and intra particular space. Selection of solvent system based on the volatility of solvent and solubility of polymer and type of method of preparation used for preparation of microspheres. Solvent should have high volatility and high polymer solubility. Jia Yu et. al were studied on mixture of methanol and methylene chloride (1: 9) as the organic phase to increase the solubility of the drug. In this process,

an increase was observed in the rate of precipitation of the polymer in the droplet–water interface; thus, the loss of drug into the outer aqueous phase was minimized, resulting in homogeneous and smaller particles [22]. Bodmeier et. al found that methylene chloride resulted in higher encapsulation efficiency as compared with chloroform or benzene, even though methylene chloride was a better solvent for poly (lactic acid) (PLA) than the others. Methylene chloride is more soluble in water than chloroform or benzene. The 'high' solubility allowed relatively fast mass-transfer between the dispersed and the continuous phases and led to fast precipitation of the polymer. The significance of solubility of the organic solvent in water was also confirmed by the fact that the addition of water-miscible co-solvents such as acetone, methanol, ethyl acetate, or dimethyl sulfoxide (DMSO) contributed to increase of the encapsulation efficiency. Knowing that the methanol is a non-solvent for PLA and a water-miscible solvent, it can be assumed that methanol played a dual function in facilitating the polymer precipitation: First, the presence of methanol in the dispersed phase decreased the polymer solubility in the dispersed phase[23].



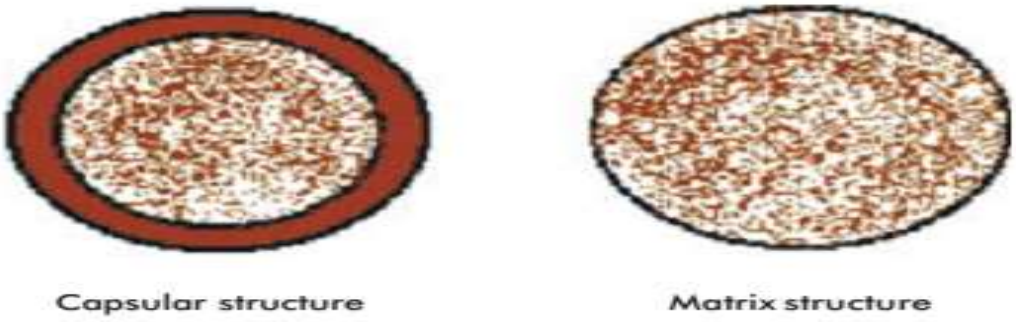


Figure 1. Types of structures of the particle resulting from the microencapsulation process of a liquid material.

Ratio of Dispersed Phase to Continuous Phase

(D/C ratio): Additionally, the surface of microspheres was smoother at lower D/C ratios, probably due to the faster solidification rate. It has been reported that the porosity in a system of microspheres is determined during microspheres hardening as the organic solvent evaporates during preparation[24]. Due to the fast solidification of the polymer, particle size increased with increasing volume of the continuous phase. Microparticles generated from a low DP/CP ratio had a lower bulk density which the authors interpret as an indication of higher porosity of the polymer matrix. Encapsulation efficiency and particle size increase as the volume of the continuous phase increases [25,26,27]. For example, the encapsulation efficiency increased more than twice as the ratio of the dispersed phase to the continuous phase (DP/CP ratio) decreased from 1/50 to 1/ 300 ,On the other hand, a different example shows that a higher DP/CP ratio resulted in increased porosity, providing a large specific surface area. Continuous phase containing a large amount of water resulted in faster polymer precipitation and therefore less porous spheres were formed[28]. Encapsulation efficiency and particle size increase as the volume of the continuous phase increases in case of O/W emulsification method. For example, the encapsulation efficiency increased more than twice as the ratio of the dispersed phase to the continuous phase (DP/CP ratio) decreased from 1/50 to 1/300. It is likely that a large volume of continuous phase provides a high concentration gradient of the organic solvent across the phase boundary by diluting the solvent, leading to fast solidification of the microparticles. On the other hand, when the continuous phase was 80 ml or more, the microspheres hardened quickly and formed irregular precipitates. This is because the large volume of continuous phase provided nearly a sink condition for ethyl acetate and extracted the solvent instantly. Due to the fast solidification of the polymer, particle size increased with increasing volume of the continuous phase. As volume of continuous phase is increased, the size of microspheres decreased which results in decrease in loading efficiency, less mucoadhesion time

and faster drug release .In fact, porosity increases with increasing DP/CP ratio, ie. decreasing rate of the polymer precipitation.

Encapsulation Efficiency

The encapsulation efficiency of the drug depended on the solubility of the drug in the solvent and continuous phase. Using higher amounts of the drug caused a slight increase is viscosity of dispersed phase. Most attempts to increase encapsulation efficiency are based on a common idea that fast polymer precipitation on the surface of the dispersed phase can prevent drug loss into the continuous phase .On the other hand, when solidification of the dispersed phase is delayed; encapsulation efficiency becomes low because more drugs diffuse into the continuous phase. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymer as the volume of processing medium was increased from 100 ml to 200 ml the entrapment efficiency significantly decreased from 32% to 17%. Entrapment efficiency of polypeptides was increased by enhancing the viscosity build up. The percentage yield was decreased at a low concentration of polymer [1:2 ratio]; at higher stirring rate [1200 rpm]; and at high surfactant concentration [0.6%] This reduction in the percentage yield in these cases may be due to; a) the small size of microsphere obtained in all these cases which may loss during filtration and washing processes, b) increasing surfactant concentration results in a brittle surface of microspheres, which lead to a drug loss during washing of microspheres. As the volume of processing medium was increased, the emulsion droplets probably moved freely in the medium, thus reducing collision induced aggregation and yielding small and uniform microspheres. This could also be the reason for higher drug extraction into the processing medium resulting in lower entrapment efficiency. Reason for less entrapment also may be due to the higher migration of drug to the surface of the microspheres during solvent evaporation from the freely moved emulsion droplets in large volume of processing medium. EE% increased significantly as the drug: polymer ratio varied from 1:1 to 1:5 which can be explained by increased viscosity of the organic phase and dense internal structure, therefore less drug loss during evaporation [29,30]. The results indicate that there was a significant decrease [P> 0.05] in the EE% with increasing the stirring rate for preparation of microspheres. The encapsulation increased with decreasing the stirring rate. A probably explanation is that, the surface area of large particles is lower which lead to less transport of the drug into the external aqueous phase.

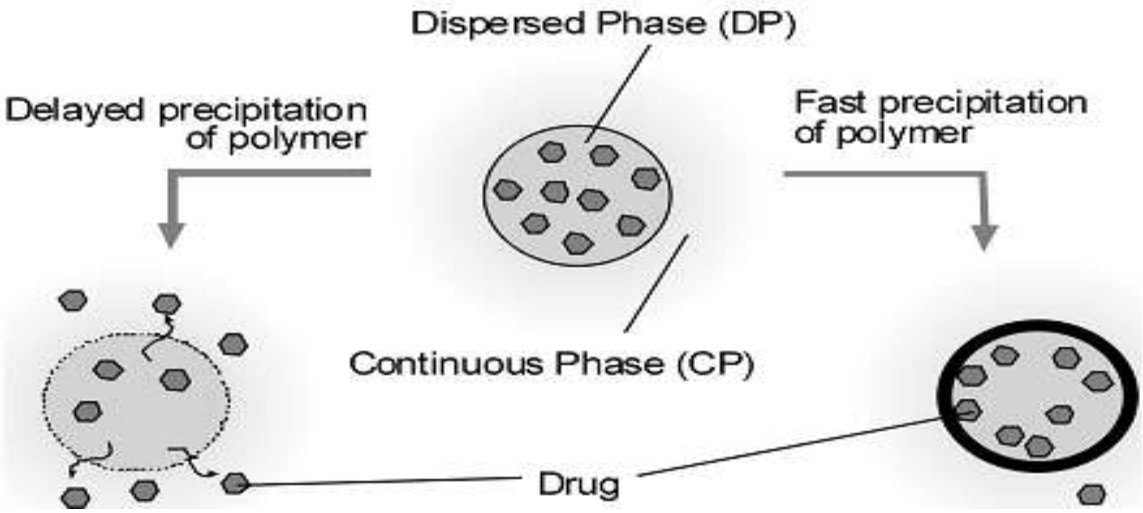


Figure 2: Schematic description of the rationale for encapsulation efficiency

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 (P^H 12, in which quinidine sulfate is insoluble than in the neutral continuous phase).

Effect of Concentration of Emulsifier

At optimum concentration (Tween 80) get fine stable dispersion, but below this droplets are fused to form larger globules that requires lower emulsifier concentration to impart stabilization and above optimum concentration particle size wise no significant impact with rough surface particles were observed. Results from this investigation shows that increase in concentration of Span -85 decreases 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 (avoid coalescence) and results in smaller microspheres. Loss of drug from surface of small microspheres is more as compared to larger microspheres during washing[30]. Lakshmana Prabu S et. al concluded that, amount of PVA as an emulsifying agent did not influence the drug loading and entrapment efficiency of microspheres however the particle size of microspheres is seen to be dependent on the PVA concentration in the continuous phase. The results revealed that on increasing PVA concentration, more PVA molecules may overlay the surface of the droplets, providing an increased protection of the droplets against coalescence resulting in the production of small

emulsion droplets. Since microspheres were formed from emulsion droplets after solvent evaporation, their size was dependent on the size of emulsion droplets[31]. As the concentration of Span 80 increased a faster drug release was observed. This may be attributed to the presence of greater amount of free drug on the surface of the microspheres with increasing the concentration of Span 80 used for secondary emulsification process when 0.25% span 80 was incorporated, microspheres were not formed because the low emulsifier content failed to prevent droplet coalescence in the oil medium; as a result mean particle size was increased. The type and concentration of emulsifier has a key role to play in the preparation of microspheres. Spherical microspheres were formed when the Span 80 content was at 0.5%. The *n*-hexane, non-solvent for the polymer added at this stage may lead to a quick precipitation of the polymer leaving the surface of microspheres porous.

Effect Concentration of Cross Linking Agent

Patel et. al has studied effect of cross linking agent on loading efficiency of mucoadhesive microspheres of glipzide. Result from this study showed significant effect on the percentage mucoadhesion and drug entrapment efficiency of microspheres. 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[32]. Increase in the cross linking time favored controlled release of drug from the microspheres. This is also due to the hardening of the spheres as a result of longer cross linking time. However, excessively high polymer content would hinder homogeneous distribution of the added cross linking agent (glutaraldehyde) leading to the formation of larger particles with reduced drug content and entrapment efficiency.

Solvent Combination

Selection of solvent is very important for microspheres preparation. A mixture of ethanol and dichloromethane used for this microspheres preparation as solvent. Because when non- polar solvent dichloromethane used alone the polymer get precipitated rapidly at the time of mixing with water. So to reduce the non polarity of the dichloromethane, ethanol was added to that solvent. During microspheres formation ethanol gets diffused in to the water and dichloromethane was evaporated.

Effect of Stirring Time

In microsphere preparation, when stirring time was increased from 30 min to 60 and then 90 min, the yield and entrapment efficiency was decreased due to increasing the partition of drug to the continuous medium with increasing stirring time. Because of the turbulence of aqueous phase, the

polymer stuck around the paddle of the mixer and a great loss of the polymer was indicated so optimum speed is advisable.

Effect of Continuous Phase Volume (Aqueous Phase)

Marimuthu S et al., has studied in cefuroxime axetil floating microspheres microspheres preparation, when the continuous phase volume was increased from 50 ml to 100 ml and150ml,the percentage yield and entrapment efficiency of drug was decreased gradually. This may dueto increasing the partition of drug in to the continuous phase when the continuous phase volume was increased. When continuous phase volume increased the particle size decreased and buoyancy of microspheres increased. Larger phase of continuous phase result in less collision between emulsion droplets and fine dispersement of dispersion thereby yielding small and uniform microspheres(solvent evaporation technique). In-vitro drug release from the microspheres was slightly increased with increasing the continuous phase volume in microspheres preparation process. This may due to the more porous nature of the microspheres.

Effect of Internal Phase Volume (Organic Phase)

In microspheres preparation, when the volume of internal phase increased from 5ml, 10ml and 15ml the yield was increased because when less amount of internal phase solvent employed that evaporated rapidly before mixing with continuous phase so it formed as a fibers and aggregates which reduce the yield of microspheres. Particle size of the microspheres also decreased with increasing internal phase volume. This can be explained as in less amount of solvent the polymer solution was more viscous which produce larger droplet when poured into the continuous phase, so particle size was increased. Entrapment efficiency of drug in microspheres was decreased with increasing the internal phase volume. This may due to the movement of drug particle from internal phase to continuous phase was increased because of decreasing the viscosity of drug-polymer solution. So the entrapment efficiency was decreased.

Drug Loading

An increase in initial loading of the drug increases nanoparticles mean diameter and poly dispersity index. Greater amount of drug results in more viscous dispersed phase, making difficult the mutual dispersion of the phases and forming larger particle although encapsulation efficiency was practically same .Several factors affect the entrapment efficiency of drugs in chitosan microspheres, e.g., nature of drug, chitosan concentration, drug polymer ratio, stirring speed, etc. Beyond increased amount of polymer decreases entrapment efficiency due to the aggregation of polymer matrix as a consequence of higher viscosity of internal phase in which drug did not

dispersed uniformly in smaller droplets upon induced shear for preparation of spheres (solvent evaporation technique).

HLB System

Properties of microspheres are affected by both HLB and surfactants. At the same HLB, surfactants consist of more fatty acid chains fabricate microspheres of larger and have higher drug contents. In contrast, surfactants with longer polyoxy ethylene chain produce smaller microspheres. Within same blend of surfactants, HLB produces marked variation in sizes of the microspheres but, drug content is, however, not definite. The rate of drug release generally retard by surfactants with low HLB. Addition of hydrophilic surfactants to aqueous phase containing the drug produces larger microspheres having lower drug encapsulation efficiency. Increasing the PVA concentration in the external aqueous phase ensures good emulsification process and results in both size reduction and lower poly dispersity index. Higher concentration of surfactant may result in a more stable emulsion which hinders the mass transfer of insulin with surrounding leading to a more even and homogenous distribution of protein within the interior of PLGA microspheres.

Solvent Evaporation Rate

Microspheres obtained by fast rate of solvent evaporation (reducing ambient pressure) gives smooth surface with smaller particle size and lower drug encapsulation efficiency than microspheres by normal rate of solvent evaporation.

pH of Processing Environment

High encapsulation efficiencies were obtained when the salts were added to both the internal and external aqueous phases while encapsulation efficiencies were significantly lower when salt being added to only the internal aqueous phase. Increase in pH of external aqueous phase decreases the degree of ionization and solubility of drug which results in increasing the drug entrapment.

Effect of Pressure

Izumikawa et. al. has revealed that drug encapsulation efficiency was greater for microspheres that have been prepared using solvent evaporation at a reduced pressure than for those prepared at atmospheric pressure. In order to verify the influence of organic solvent evaporation rate a vacuum rotary evaporator presented nanoparticles of small diameter than the particles obtained by magnetic stirring method. The reason or the formation of smaller particle is the higher solvent front kinetic energy. The microspheres made by reducing pressure have an apparent smooth surface and smaller size than made at atmospheric pressure. Reduced pressure can improve the drug encapsulation efficiency.

Processing Temperature

Gradually increasing preparation temperature leads to decrease in particle size. This is due to the emulsion at high temperature is less viscous, thus it is much easier for the emulsion to be broken up into smaller droplets at the same power of mixing input. The temperature of the dispersing medium is an important factor in the formation of microspheres as it controls the evaporation rate of the solvents. Microspheres prepared at low temperature ($10^{°C}$) were crushed and irregularly shaped. The shell of the microsphere turns translucent during the process, due to slower diffusion rate of ethanol and dichloromethane. Microspheres fabricated at low temperature (15, 22°C) by solvent evaporation method exhibited similar steady drug release rates. However, microspheres formed at higher temperature exhibited low release rates after their initial drug release. Microspheres prepared at high temperature were found to be a uniform internal pore distribution and a very thin dense skin layer; it might be due to the faster diffusion of alcohol in the droplet into aqueous phase and evaporation of dichloromethane immediately after introducing it into the medium[33]. Whereas microsphere prepared at lower temperature showed a thick but porous skin layer and bigger pores in the middle of the sphere. Microspheres formed at 33°C experienced the highest initial burst release. However higher temperature yield larger size of microsphere, probably due to rapid solvent evaporation microsphere fabricated at low temperatures, exhibit similar, steady rate but microspheres formed at higher temperature give very low release rates after their initial release. At low preparation temperature gives the fastest initial but the lowest overall shrinking rate, uniform internal pore distribution, and a very thin dense skin layer, while at high temperature the lowest initial yet the highest overall shrinking rate, thicker but porous skin layer and bigger pores at the middle of the sphere.

Addition of Polymer Solution

As reported that, the high surface tension of water caused the solidification and aggregation of polymer on the surface of aqueous phase. To minimize the contact of polymer solution with the air-water interface and to develop a continuous process for preparing microspheres, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the introduction of the polymer solution through the glass tube without contacting the surface of water. This method improved the yield of microspheres and reduced the extent of aggregate formation. Particle size and bulk density also varied according to the polymer. Since polymers having higher solubilities in methylene chloride stayed longer in the semi solid state, the dispersed phase became more concentrated before it completely solidified, resulting in denser microparticles.

Size of Sphere

It was found that particle size was dependent on drug-polymer ratio, volume of ethanol, type of polymer and concentration of polyvinyl alcohol increasing the polymer load led to a more viscous solution by quasi emulsion technique. When the viscous polymeric solution was poured into the aqueous phase, larger droplets and thus larger microspheres were formed. It was observed that at higher drug concentration, the mean particle size of the microspheres is high but increasing the stirring speed and emulsifier content, resulted in smaller mean particle size of microspheres (Double Emulsion Solvent Diffusion Method). Larger particles developed due to increased viscosity of the medium with an increasing higher polymeric concentration. This is because at higher viscosities there is enhanced interfacial tension and diminished shearing efficiency. This may be due to following reasons:

a) Increase in the wall thickness of the microspheres arising due to the increase in polymer conc. leading to increase the length of diffusional pathway through the polymer membrane

b) Increase polymer conc. Lead to decrease amount of drug close to surface.

c) As the conc. Of polymer increase, large amount of drug got bind in the polymer matrix as a result the rate of release decrease.

It was observed that the surface of microspheres prepared with Eudragit RS was smoother than that prepared with Eudragit RL. The effect of retardation on the dissolution rate depended on the type of Eudragit. As drug release rates were very slow and incomplete from Eudragit RS microspheres, the same formulation was prepared using Eudragit RL as polymer and different drug release profile was observed.

Effect of 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.

Solubility of Organic Solvent in Water

The ‘high’ solubility allowed relatively fast mass-transfer between the dispersed and the continuous phases and led to fast precipitation of the polymer. First, the presence of methanol (for PLA) in the dispersed phase decreased the polymer solubility in the dispersed phase[32]. Second, as a water-miscible solvent, methanol facilitated diffusion of water into the dispersed phase. Encapsulation efficiency increased, and initial burst decreased as the volume fraction of DMSO (for solubility of PLGA) in the co-solvent system increased. Particle size increased, and density of

the microparticle matrix decreased with increasing DMSO. Overall, these results indicate that the presence of DMSO increased the hydrophilicity of the solvent system and allowed fast extraction of the solvent into the continuous phase, which led to higher encapsulation efficiency and larger particle size[33].

Influence of Homogenization Speed on Microsphere Size

It is obvious that the rotation speed of propeller affects yield and size distribution of microspheres. As the rotation speed of propeller increases, the average particle size decreases particle size decreases with increasing homogenization speed as the homogenization speed increases, the shear stress increases and the established balance between tangential stress at the droplet interface impacted by the homogenizer and interfacial tension is going to be altered. The larger tangential stress leads to a reduction in droplet size, while the homogenization speed affects the relative viscosity of the emulsion. Typically, the viscosity reduction at a higher rotational speed is responsible for a decrease in particle size. While homogenization speed was found to be the dominant factor for the sizing of microspheres, homogenization times, at least at high homogenization speeds of 26,000 rpm did not significantly change the final microsphere size. At stirrer speed of 1500 rpm , the resulting high turbulence, caused frothing and adhesion to the container wall. Therefore, the mean particle size of microspheres decreased. The desired spherical and not aggregated microspheres were obtained at stirring speeds of 1000 rpm, any increase in mean particle size at lower stirring rate as 500 rpm can be attributed to increased tendency of globules to coalescence and aggregate. Microspheres prepared by a higher stirring rate showed smaller sized particles and lower drug content but high shearing force needed to breakdown the drug-polymer droplets into smaller particles and the size of the microspheres reduced and thus changed the flow properties of the microspheres. The reduction of mean particle size of microparticles could facilitate higher rate of drug diffusion from larger surface area provided by the smaller microparticles. The results also indicate that, increasing the stirring rate resulted in increase in the rate of drug release. These may be due to that smaller particle size microspheres are produced at higher stirring rates, which possess a large surface area leading to higher release rate. B- microsphere prepared at higher stirring rate are more porous, exhibit fast release of drug, release more than 90% in 7 hours, which was not acceptable to the desired criteria for sustained release.

Influence of Pva Concentration and Evaporation Speed on Microsphere Size

A wide range of substances, such as PVA, methyl cellulose, sorbitan mono oleate, sodium alginate, gelatin, and sodium dodecyl sulfate, have been used for the stabilization of polymeric

microspheres produced by emulsion solvent evaporation techniques . In this study, PVA was used as the stabilizing and emulsifying agent. When the concentration of PVA was varied from 0.5 and 2 % (w/v), the microsphere size decrease. The effect was probably mainly due to the increasing viscosity of the PVA solution. During the emulsion formation, the droplets get smaller and smaller under the strong shear stress, while the droplets tend to coalesce again to reduce their surface energy. The presence of surfactant molecules can stabilize the emulsion by forming a protective layer around the droplets thus impeding droplet coalescence and coagulation

Influence of Oil Phase on Microsphere Size

Mean particle size increased with increase in polymer content of the microspheres. It seems that when polymer content increased, a more viscous internal phase manifested during the emulsification process, and was poorly dispersed in the external phase. The result is the formation of large microspheres .The polymer concentration in the oil phase affects the microsphere size and loading efficiency. The higher the viscosity of the oil phase, the higher the forces that need to be overcome to form fine particles. Highly viscous polymer solutions have been reported to produce microspheres with a dense core, which in turn show decreased initial protein burst release [34, 35], Furthermore, the viscosity of the polymer solution affects other microsphere properties such as drug content, specific surface area, and porosity, due to its effect on the rate of solvent extraction. The viscosity characterization is thus an important part of the microsphere process development. The effect of oil phase volume on microsphere size was studied by keeping the amount of PLGA constant and increasing the volume of the oil phase from 3.0 to 6.0 ml. The size of microspheres dropped from 1.78 to 1.21 μm this may be due to the fact that an increase in the volume of the oil phase generates a less viscous oil phase, from which droplets break off more easily into smaller droplets, thus generating smaller microspheres. Many of the microspheres were distorted and oval in shape. This might be due to a much faster precipitation time of the polymer at the polymer/solvent interface because of EA's lower boiling point and higher water solubility (about 10%). Thus the composition of the solvent plays a key role in the formation of microspheres and affects the solidification time and size of the microspheres.[36]

Drug Release

The rate and amount of drug release is increased as the concentration of the surfactant is increased at constant drug: polymer ratio. This is due to the increase in wettability and better solvent penetration as the surfactant is increased.

CONCLUSION

The present article provided a review of several formulation variables that affect encapsulation efficiency, selection criteria for ratio of oily and aqueous phase.

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