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Microencapsulation technique by solvent evaporation method (Study of effect of process variables)

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Abstract

The preparation of microsphere by solvent evaporation method has been studied extensively to prepare a microsphere using biodegradable polymer. The properties of biodegradable microsphere of poly (lactic acid) (PLA) and (acid lactic- co-glycolic) (PLGA) have been extensively investigated. The encapsulation of highly water soluble compounds including proteins and peptides is providing challenges to the pharmaceutics person. The successful encapsulation of such entities requires high drug loading in the microsphere, prevention of protein degradation by the encapsulation method, and predictable release of the drug compound from the microsphere. Multiple emulsion techniques and some other innovative modifications have been made to the conventional solvent evaporation process. A several process variable affecting the quality of product has been studies in this review.

Key-Words: Microencapsulation, Method, Process, Variables

Introduction[1-2]

Control drug delivery, using biodegradable polymer has focused a lot of attention in last two decades. Microencapsulation is a process by which solid, liquid or even gaseous particles are coated with a continuous film of polymeric material. These particles are in the size range of 1-1000µm and are widely used as a drug carrier for controlled release. The first research in the microencapsulation process for pharmaceutical products was published by Bungen burg de jong and Kan in 1931 and dealt with the preparation of gelatin spheres and the use of gelatin coacervation process .Microspheres are formulated so as to provide constant drug concentration in blood thereby increasing patent compliance, decrease dose and toxicity. They also protect drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein. Other reasons for microencapsulation may be summarized as –the taste and odor of many drugs can be masked, liquid drugs can be converted in to a free flowing powder, incompatibility among the drugs can be prevented, the site of absorption can be altered. Bakes and Anderson reported that the stability of Vitamin A palmitate can be enhanced by formulating it in the form of microspheres.

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Drug release mechanism from microsphere may be classified as -: Degradation controlled monolithic system – The drug is dissolved in matrix and release is depended on degradation of the polymer matrix. The diffusion of the drug is slow as compared with the degradation of matrix; Diffusion controlled monolithic system- Here the drug is released by diffusion prior to or simultaneously with the degradation of polymer matrix; Diffusion controlled reservoir system – Here the active drug is encapsulated by a rate controlled membrane through which the drug diffuses. The polymeric membrane erodes only the complete delivery of drug; Erosion – The coated polymeric material like beeswax & stearyl alcohol due to pH and enzymatic hydrolysis.

Several technique of microsphere has been reported like -:

- Solvent diffusion method
- Spray drying method
- Spray congealing method
- Coacervation phase separation method
- Polymerization
- Emulsion solvent evaporation

However solvent evaporation techniques have become more useful method as compared to other methods. Controlled particle sizes in the nano to micrometer range can be achieved this method, but there is a need of careful selection of encapsulation materials and various conditions in order to achieve high

encapsulation efficiency and a low residual solvent content. Several process variables had been identified by researchers which could affect the formulation of microsphere by solvent evaporation method such as type of solvent, volume of solvent, drug to polymer ratio, rate of solvent removal, effect of internal aqueous phase volume in case of solvent evaporation followed by multiple emulsion, effect of addition of buffer or salts to the internal or external phase which can affect the size of microsphere and also the release pattern of the drug from microsphere. The need to optimize the release rate profile of drug from polymeric microsphere is a significant problem. So change in one of the above parameter causes the significant change in drugs loading & desired release rate. So our aim is to study the different process variables shown above to optimize formulation, obtain high drug loading ability and to predict the release pattern. Following table shows different techniques of microencapsulation:

Method name	Applicable material	Particle size	Production scale	Process reproducibility preparation	Time required	Coating factor	Operation skill required
Air suspension	Solids	35-5000	Pilot scale	Moderate	High	High	High
Coacervation & phase separation	Solid /liquid	2-5000	Lab scale	Good	Less	Less	Less
Multiorifice centrifugal	Solid /liquid	1-5000	Pilot scale	Moderate	High	High	High
Pan coating	Solid	600-5000	Pilot scale	Moderate	High	High	High
Solvent evaporation	Solids /liquid	600-5000	Lab scale	Good	Less	Less	Less
Spray drying & spray congealing	Solids /liquids	600	Pilot scale	Moderate	High	High	High

Fig. 1: Different techniques of microencapsulation.

Differenet techniques and steps involved in microencapsulation process

Techniques of microencapsulation

Oil/Water emulsion followed by solvent evaporation

The drug substance is either dispersed or dissolved in the polymer/solvent system. Then it is added to the aqueous phase by continuous agitation. Agitation of the system is continued until the solvent partitions into the aqueous phase and is removed by evaporation. This process results in hardened microsphere which contains the active moiety that is drug. Several methods have been utilized to achieve dispersion of the oil phase in the continuous phase. The most common method is the use of a propeller type blade attached to a variable speed motor. Since high shear is used to produce the emulsion, the resultant product has a much smaller particle size than the emulsion produced by conventional agitation. Other method includes the use of a micro fluidizer to produce micro-emulsions, sonication and potentiometrics dispersion.

1.2. Water-oil-water multiple emulsion system

This method for preparation of microsphere was reported to overcome the problem of low encapsulation efficiency of water soluble drug prepared by conventional water/oil emulsion solvent evaporation method.

Polymer [generally Poly (lactic-co-glycolic acid) (PLGA)] is dissolved in organic phase most commonly DCM (Dichloro methane). In this organic phase,

Disadvantage

A major problem with this technique is a poor encapsulation efficiency of moderately water soluble and water soluble compounds, which partitioned out from the organic dispersed phase into the aqueous continuous phase. Successfully entrapment of drug within the microspheres is thus highly dependent on solubility in the aqueous phase. Water soluble drugs (e.g. theophylline, caffeine and salicylic acid)could not be entrapped within the poly (lactic acid) (PLA) microsphere using an Oil/Water emulsion method, while drugs with low water solubility, such as Diazepam, Hydrocortisone and Progesterone were successfully retained within the microspheres.

aqueous drug solution is emulsified using high speed homogenizer operating around 15000-20000 rpm for about 30s to prepare water[1] /oil (w^1/o) primary emulsion. This primary emulsion is added to external aqueous phase containing surfactant (most widely poly vinyl alcohol is used to prepare $w^1/o/w^2$ emulsion) at homogenizer speed around 8000 rpm for 30s and then stirred at 300 rpm for 3hour at room temperature for permit evaporation of DCM or it can be also performed under vacuum. The microsphere obtained is collected by ultracentrifugation, filtration and then lyophilized; lyophilisation decreases the burst effect. This is the standard protocol to prepare microsphere by this method. But it may be changed from drug to drug to obtain acceptable microsphere size and drug release.

Multiple emulsion of the Water/Oil/Oil or Water/Oil/Oil/Oil type

Iwata and Mc Ginity developed a multiple emulsion of the W/O/O/O type . Multiphase microsphere of PLGA containing water-in oil (W/O) emulsions was prepared by a multiple emulsion solvent evaporation techniques. Acetonitrile was used as the solvent for the polymer, and light mineral oil comprised the continuous phase for the encapsulation procedure. Drug loading efficiencies of model water soluble compounds ranged from 80 to 100% of theoretical, based on specific preparative conditions. Scanning electron microscopy of transverse cross sections of the multiphase microsphere of thee W/O/O/O type belonged to the class of reservoir type drug delivery devices. Utilization of this type of multiple emulsion system allows the encapsulation of the primary water in oil emulsion within a polymeric microsphere. The oil in the primary emulsion prevents contact between the internalized protein and the polymer/solvent system prevents possible denaturisation of the protein by the polymer or the solvent. Likewise, the possibility of polymeric degradation due to reactive proteins or drug compounds is also limited

A modified water-in-oil-in-water ($W_1/O/W_2$) double emulsion solvent evaporation

Taek Kyoung Kim et al has developed Gas foamed open porous biodegradable polymeric microsphere. Highly opened porous biodegradable polymeric microspheres were fabricated for use as injectable scaffold micro carriers for cell delivery. They modified water-in-oil-in-water ($W_1/O/W_2$) double emulsion solvent evaporation method for producing the microspheres .When an effervescent salt, ammonium bicarbonate is added in to the primary W^1 droplets, carbon dioxide and ammonia gas bubbles were spontaneously produced during the solvent evaporation process, that stabilized the primary emulsion as well as created well inter-connected pores in the resultant microspheres. The porous microspheres fabricated under various gas foaming conditions were characterized. The size of the surface pores formed under the various gas foaming conditions became as large as 20µm in diameter. As the concentration of ammonium bicarbonate increased, the diameter which was sufficient enough for cell infiltration and seeding. These porous scaffold microspheres could be potentially utilized for cultivating cells in a suspension manner and for delivering the seeded cells to the tissue defect site in an injectable manner.

Micro sphere preparation by solvent evaporation method basically involves 4 major steps

Incorporation of medicaments

The polymer is dissolved in a suitable water immiscible solvent, & the medicament is dispersed or dissolved in this polymeric solution.

Bioactive compound is added in to the solution of the matrix material by either co dissolution in a common solvent, dispersion of finely pulverized solid material or emulsification of an aqueous solution of the bioactive compound immiscible with the matrix material solution

Dispersion of solid or dissolved bioactive material in to the matrix solution can impeller or static mixing , high speed-stator mixing or microfluidasation

Droplet formation

This is the step that determines the size of resulting microspheres. The size of microsphere affects the rate of drug release and drug encapsulation efficiency. The following procedures are used in droplet formation.

Stirring

The extraction phase is filled into a vessel & agitated by an impeller. The drug/matrix dispersion us then added, drop wise or all at once, under agitation at a speed sufficient to reach the desired droplet size.

Static mixing

Static mixer consist of baffles or other flow obstacles installed in a tube. The baffle arrangement repeatedly splits and recombines the stream of fluid passing through the tube.

Extrusion

It involves feeding of drug/matrix dispersion through single or multichannel pathways directly into the continuous extraction phase. When drug/ matrix dispersion leaves the pathways, discrete droplets are formed within the slow flowing continuous phase. In extrusion, flow is laminar, the droplets are formed at the site of introduction of drug/matrix dispersion into continuous phase, due to which there is no effect on size of droplets formed thereafter. Where as in static mixing, turbulent flow occur which constantly act on

the disperse phase and thus there is a continuous change in the size of droplets.

Dripping

Microsphere has been prepared by dripping 10% and 15%(w/w) solution of poly(ethylene-co-acetate) in DCM, containing dispersed protein particles from a needle into an electric field. The droplet formed was dethatched from the needle by electrostatic forces.

Jet Excitation

The vibration of a liquid jet for its disruption into droplets was originally studied by Lord Rayleigh in late 19th century . A longitudinal oscillation imposed on a liquid stream causes periodic surface instabilities that result into droplet formation. This principle was recently used to produce uniform PLGA micro particles.

Solvent Removal

Solvent removal can be achieved either by evaporation or extraction. In both processes the drug/matrix dispersion should be slightly soluble in the continuous phase so that partitioning into continuous phase can occur that leads to precipitation of the matrix material. The two ways of solvent removal are as followed

Solvent Evaporation

In this method, the capacity of the continuous phase is insufficient to dissolves the entire volume of disperse phase solvent. Thus, solvent evaporates from the surface of the dispersion to obtain hardened microsphere.

Solvent Extraction

This is a two step process. Firstly, the drug/matrix dispersion is mixed with a small quantity of continuous phase to yield desired size of droplets. Then secondly further more continuous phase and/or additional extraction agents are added at an amount sufficient to absorb the entire solvent leaching from droplets of drug/matrix. This results into formation of solid microspheres.

Microsphere drying

Solidified microsphere from the continuous phase is either by filtration or centrifugation. Then the particles are rinsed with suitable liquids to remove adhering substance such as dispersion stabilizers or non encapsulated drug Finally these microsphere are dried at elevated temperature or under reduced pressure to yield free flowing powder.

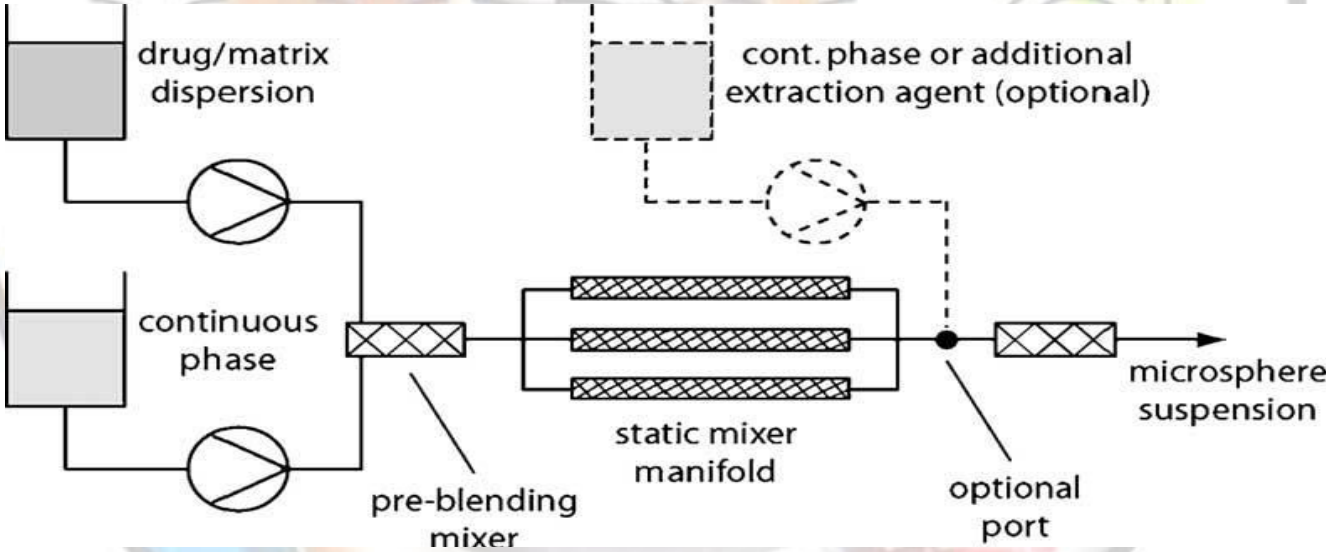

Fig. 2: Parallel installation of several static mixers for scale-up of microsphere production.

A study of process variables

Effect of polymer

Polymer used as matrix for drug delivery can be classified into three basic groups- : Biodegradable polymer, non biodegradable polymer, water soluble polymer. Here only biodegradable polymer is discussed. As the other two types are not used in microsphere formation by solvent evaporation due to incompatibility and toxicity produced by non biodegradable polymer. Further biodegradable polymer used can be classified into-:

Natural polymer

Animal protein and animal polysaccharides – e.g. Albumin, collagen, gelatin, fibrinogen, casein, fibrin, chitin, chitosun, haluronic acid.

Plant polysaccharides- e.g. Starch, dextrin, alginic acid.

Synthetic polymer

e.g. poly (lactic acid), poly (lactic/glycolic acid), poly (ß-hydroxybutyric acid), poly ortho ester, poly alkyl cyano arylate.

Owing to the excellent biocompatibility property of the biodegradable polyesters poly(lactic acid) and poly(lactic-co-glycolic acid)(PLGA), these are the most widely used biomaterials for the microencapsulation of therapeutics and antigens.

Effect of drug to polymer ratio

For the entrapment of bovine serum albumin (BSA) into poly (methyl methacrylate)(PMMA) microspheres, a ratio of less than 1:10 was suggested to yield protein loadings of >80%

A higher load of bioactive material is likely to decrease the encapsulation efficiencies of proteins and peptides in PLGA and increase the 24 hrs ("burst") drug release

In some cases, increase in drug content, increases the entrapment efficiency e.g. an increase in entrapment efficiency ovalbumin (ova) from 40% to 98% with an increase in actual ova content from 7% to 16%(w/w) .Cavalier et al (1986) studied the preparation of PLA microcapsules containing hydrocortisone using polyvinyl alcohol (PVA) (partially hydrolyzed 88%) and methyl cellulose (400cps and 10cps grades) as colloidal emulsifiers. They reported that when the drug/polymer ratio was less than 0.4, microcapsules could be prepared using PVA (0.1%in water) only and in regular dimensions. But when this ratio exceeded 0.6, irregular and large aggregated microcapsules were formed due to the formation of unstable emulsion.

Effect of organic solvents

R. Bodmeier and J.W .Mc. Ginity performed experiment by preparing quinidine sulphate microsphere using o/w emulsion solvent evaporation method to know the effect of solvent, volume of solvent on drug loading and observed that the successful entrapment of drug within microsphere is associated with a fast rate of precipitation of the polymer from the organic solvent phase; a low water solubility of the drug in the aqueous phase; and a high concentration of the polymer in the organic phase .

It was initially expected that favorable solubility of the drug in the organic solvent would enhance the drug content in the microsphere. The solubility of quinidine sulphate in methylene chloride and chloroform were determined to be 9.16 and 97.57 g/l respectively. Although the solubility of quinidine sulphate in chloroform was found to be 10 times higher than n methylene chloride and chloroform, drug content was found to be higher in microspheres prepared with methylene chloride as compared to microsphere prepared with chloroform. This showed that there was another factor which was affecting entrapped drug content to be considered.

An important factor in determining the rate of precipitation is the water solubility of the organic solvent used for the preparation of microsphere solvent diffusion into the aqueous phase depends on the water solubility of the organic solvent & its removal from the water solubility of the organic solvent and its removal from the water/air interface by evaporation. Methylene chloride has the highest water solubility of the organic solvents forming microsphere as well as the lowest heat of evaporation. Solvent with very low water solubility like benzene and chloroform diffused very slowly into the aqueous phase. The droplets were in the liquid state for a long period of a time and drug could be easily diffuse acrossed the non precipitated droplet surface to aqueous phase resulted in to lower drug content. The significance of solubility of the organic solvent in water was also confirmed by the fact that the addition of water miscible co-solvents like acetone, methanol, ethyl acetate, increased the encapsulation efficiency. As 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. Firstly, the presence of methanol in the dispersed phase decreased the polymer solubility in the dispersed phase . Secondly water miscible solvent, methanol facilitated diffusion of water into dispersed phase.

Effect of molecular weight of the polymer

X. Fu et al developed a long acting injectable Huperzine A-PLGA microsphere for the chronic therapy of Alzheimer's disease. These microspheres were prepared by solvent extraction evaporation method. The microsphere morphology was studied by scanning electron microscopy. It was observed that the PLGA 15000 microspheres possessed a smooth and regular particle size of around 50µm. The encapsulation percentage & of microsphere prepared from PLGA 15000, 20,000, and 30,000 were 62.75%, 27.52% and 16.63% respectively .The encapsulation efficiency of the microsphere improved as the polymer concentration increased in oily phase and PVA concentration decreased in aqueous phase. It has been found that as the molecular weight increased, the drug loading capacity is increased because of stronger barrier characteristics of high molecular weight polymers

Different PLGA was taken; PLGA [50:50] (Mol.wt. 53100), loading of ovalbumin was found to be 5.3%, 7.3%, 8.5%, w/w respectively. This showed that PLGA 85.15 has highest loading molecular weight .

Effect of solubility of drug in continuous phase

Drug loss may occur to continuous phase while the dispersed phase remains in a transitional, semi-solid state. If the solubility of drug in the continuous phase is higher than in the dispersed phase, then the drug may easily diffuse into the continuous phase during this stage. It was observed that the encapsulation efficiency of quinidine sulphate was 40 times higher in alkaline (pH-12) continuous phase than in the neutral (pH-7) continuous phase because quinidine sulphate is insoluble in alkaline pH whereas very soluble in neutral pH.

Rate of solvent removal

The rate of solvent removal from microsphere prepared by the solvent evaporation method has a great impact on the physiochemical properties of the microsphere . Izumikawa et al observed a significant difference in physical property and drug release profile between progesterone loaded PLA microsphere prepared by either reduced pressure solvent evaporation or a solvent evaporation method under atmospheric conditions. Encapsulation efficiency was greater for microsphere prepared by the reduced pressure solvent extraction method (RSE) than for those prepared by the atmospheric solvent evaporation (ASE). When surface morphology of these microspheres were studied under scanning election microscopy, it indicated a porous and rough surface for RSE microsphere. The ASE microsphere exhibited peaks due to crystalline progesterone in addition to peaks due to crystalline poly (l-lactide) PLA. The RSF microspheres displayed no such peaks due to crystalline PLA which suggest that the PLA was present in the amorphous state. Additionally, the RSE microsphere exhibited no peaks corresponding to crystalline progesterone which indicated that drug was dispersed in an amorphous polymer network. It was assumed that the solvent-removal under the reduced pressure occurred too rapidly for the polymer to crystallize. Drug release from the microsphere was found to be significantly influenced by the crystallinity of the polymer matrixes, the drug release rate increased with the drug loading for both types of microsphere. For the ASE microsphere, there was a rapid release in the initial stage, and the release rate was much greater than that of the RSE microspheres. The ideal rate of solvent removal depends on a variety of factors like the types of matrix material used, drug and solvent as well as the desired drug release profile of microsphere. Like, fast microsphere solidification will be preferred if the drug easily partition into the continuous phase, whereas slow solidification favours denser over more porous microsphere, affecting the drug release.

The rate of solvent removal from the microsphere for volatile solvent is controlled by the temperatures of the microsphere dispersion. An alternative studies were done on solvent removal method under reduced pressure, in encapsulation of lidocaine or albumin in small (0.7-1.2µm) PLA microsphere. In both studies, PVP solution was used as continuous phase. Evaporation of the polymer solvent-DCM (dichloro methane) was accomplished within 6hrs at 760mm Hg or 2hrs at 460 or 160 mm Hg at 25˚C. In both the encapsulation efficiency decreased at reduced pressure whereas the drug release profile remained unaffected.

Effect of preparation temperature

Yi-Yan Yang et al studied the influence of preparation temperature on the various characteristics and release profile of poly (lactide-co-glycolide) (PLGA) microsphere. The two studies were performed for encapsulation of Bovine serum albumin (BSA) in a PLGA, both were dissolved in DCM and an aqueous PVA solution was stirred for 30 min and examined by varying temperature (4-42˚c) . The dispersion was thereafter diluted to a defined volume by further addition of continuous phase at controlled temperature. The PLGA microsphere tends to be larger when prepared at higher temperature (38 and 42˚c) and showed wider size distributions and decreased particle density as compared to microsphere prepared at lower temperature (4-33˚c). In case of PLGA microsphere , the morphology of the particle interior (honeycomb-like) and BSA encapsulation efficiency (53% to 63%) were unaffected by the preparation temperature whereas in case of PGLA-PEG blend , encapsulation efficiency was unaffected with a minimum efficiency of (15% to 63%) were unaffected by the preparation temperature whereas in case of PLGA-PEG blend, encapsulation efficiency was affected with a minimum efficiency of 15% at 22˚c, which steadily got improved (around 52%) for lower and higher temperatures.

Microsphere prepared at high temperature have a uniform internal pore distribution and a very thin dense skin layer, which microsphere prepared at lower temperature have a thick but porous skin layer and bigger pores in the middle of the sphere . Microsphere formed at 33˚c has the highest initial burst release. In term of in vitro release microsphere fabricated at low temperature (5˚, 15˚, 22˚c) exhibit similar steady rates. Microsphere formed at higher temperature however gives low release rates after their initial release. Microsphere fabricated at lower temperature solidify slower, the lower solubility and mass transfer of BSA at those temperature probably compensate for the relative ease of diffusing through the softer, less dense skin. The activity of protein also remains fairy intact at

these lower temperatures. The resultant encapsulation efficiencies for microspheres fabricated at higher or lower temperature are thus similar. The effect of temperature gradient on encapsulation of salmon calcitonin (sCT) into PLGA was also studied. The temperature gradient was used to remove the solvent, hollow microsphere with porous walls were obtained. An aqueous solution of sodium oleate was used as a continuous phase and the temperature of the resulting dispersion was increased for 30 minutes led to particle with a large empty core and a thin wall, while a gradual increase over 200 minutes resulted in increased wall thickness.

Effect of interaction between drug and polymer

A study was done which showed that the interaction between protein and polymer contributed to increase in encapsulation efficiency. The interaction between protein and polymer may be hydrophilic or hydrophobic interaction. In case of hydrophilic or ionic interaction, the protein is best encapsulated in polymers containing free carboxylic end groups whereas in case of hydrophobic interaction, relatively hydrophobic end capped polymers are more effective in increasing encapsulation efficiency for example encapsulation efficiency of salmon calcitonin (sCT) micro particles has been increased up to 60% due to the strong affinity of sCT to hydrophobic polymer PLGA, despite of the continuous phase

On the other side, such interaction between drug and polymer may limit the protein release from the microsphere

In certain cases, co-encapsulated excipient can mediate interaction between protein and polymer. Encapsulation efficiency of tetanus toxoid in PLGA increased, when gamma hydroxylpropylcyclodextrin (g-HPCD) were incorporated. It is supposed that the g-HPCD increased the interaction by involving amino acid side group of the toxoid into its cavity and simultaneously interacting with PLGA through Vander Waal and hydrogen bonding forces.

Effect of buffer or added salt

On considering the properties of somatostatin acetate-containing polylactide microsphere, Herrmann and Bodmeier prepared microsphere for encapsulation efficiency, drug release, and morphological properties. Addition of buffers or salts to the internal aqueous phase resulted in the formation of a dense and homogenous polymer matrix. Drug release profile consisted of a rapid drug release phase followed by a slow release phase. This pattern is consistent with many matrix-type drug delivery systems. In this the drug release profile can be divided into two phase; a rapid release phase representing the release of the peptide by diffusion through the polymer matrix. Lower encapsulation efficiencies were obtained with the more porous microspheres. Addition of buffer salts to the internal aqueous phase promoted an influx of water from the external phase due to a difference in osmotic pressure. This resulted in a more porous microsphere structure, faster drug release, and lower encapsulation efficiency. Ahmad Al-Maaieh and Douglas R. Flanagan found increase in microsphere drug loading by changing the aqueous solubility of both the drug and the organic solvent DCM. Quinidine sulfate solubility was depressed by either a common ion effect (Na_2So_4) or by formation of new, less soluble drug salts (e.g., bromide, perchlorate, and thiocyanate). Inorganic salts depress DCM aqueous solubility to different extents as described by the Hofmeister series. $NaClO_4$ and NaSCN depressed drug solubility to the highest extent, resulting in microspheres with high drug loading (e.g.,>90%). Other salts such as Na_2SO_4 did not depress quinidine sulphate solubility to the same extent and did not improve loading. The use of a cosolvent (ethanol) in the organic phase was found to improve drug loading and make uniform drug distribution with smooth release profiles.

Effect of internal aqueous phase volume on loading capacity

Comparatively with large volume of internal aqueous phase (500µl or 1000µl), decrease in loading efficiency of ovalbumin occurred. While using smaller of internal phase 50µl, high loading efficiency was observed. As internal phase volume is increased, thin layer of phase (methylene chloride) is formed which act as barrier for diffusion of drug to the eternal aqueous phase. Now, thinner the organic phase more will be diffusion and probability of diffusion from internal phase to external phase is increase so lower will be the loading efficiency. So, small internal phase volume was found to be beneficial to get high drug loading

Effect of external aqueous phase volume on loading capacity

Rajesh H. Parikh et al found that an increase in the volume of the external phase of the secondary emulsion lead to a decrease in the particle size of microspheres. The droplet size of the secondary emulsion may decrease because of a decrease in the frequency of collision of droplets with an increase in the volume of the external phase of the secondary emulsion. The decrease in the particle size of microspheres associated with an increase in the volume of the external phase of the secondary emulsion may attributed to a decrease in the secondary emulsion. Castellanas et al have reported similar observations.

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Effect of Stirring Speed

During droplet formation step, the stirring of impeller or baffles used, determines the size of microsphere. Increasing the mixing speed generally results in decreased microsphere mean size.

Conclusion

The emulsion solvent evaporation method for production of PLA and PGLA microsphere has been used extensively for the encapsulation of a variety of pharmaceutical compounds. The efficacy of this microencapsulation process is dependent on many factors, including organic solvent, rate of solvent removal, and amount of organic solvent or drug solubility, drug to polymer ratio, partition coefficient, polymer composition and molecular weight, and method of method of manufacture etc. These variables must be considered in order to develop a successful controlled release PLGA microsphere containing drugs.

To formulate a stable formulation of proteins and peptides are susceptible to denaturation, degradation, and conformational changes which may render them inactive. These conditions can be produced by solvent interactions, mechanical processing or an acidic environment that may be encountered during microsphere production or storage. It has been shown that certain proteins may prematurely degrade the polymer used in the microencapsulation process. In response to these concerns, innovative methods of microsphere production, such as multiple emulsion systems have been investigated.

So by taking in account this all the fact we should design the formulation to get the desire release rate and highest drug loading.

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