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REVIEW ARTICLE

Solvent evaporation as a imposing method for microencapsulation - A review

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ABSTRACT

Microencapsulation is a process from which solid, liquid or even gaseous particles are coated with a continuous film of polymeric material, having a diameter in range of 1 to 1000 µm and are widely used as drug carriers. The goal of writing this review on microencapsulation by solvent evaporation technique was to combine the recent literature with special focus on solvent evaporation technique for microencapsulation of pharmaceuticals that have recently become leading investigated technologies in the field of drug delivery development. In order to understand the microencapsulation by solvent evaporation technique, the basics point was summarized. Afterwards, we have reviewed various solvent evaporation techniques designed and developed until now. Finally, various potential factors influencing microencapsulation by solvent evaporation technique were covered in detail.

Key words: microencapsulation, Solvent evaporation, Variables, Drug delivery

INTRODUCTION:

Microencapsulation is one of the most interesting process in the area of pharmaceutical technology by which very small droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material [1-2]. The first research leading to the development of microencapsulation process for the pharmaceuticals was published by Bungen burg de Jong and Kan in 1931 and dealt with the preparation of gelatin spheres and the use of a gelatin using coacervation process [3]. The drug substances are encapsulated in a polymer-forming particle with a diameter in range of 1 to 1000 µm and are widely used as a drug carrier [4]. Microencapsulation technology used for protection of the drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste, conversion of liquid drugs in a free flowing powders, prevention of vaporization of many volatile drugs, *etc*. [1,4]. Microcapsules provide constant drug concentration in blood thereby increasing patent compliance, decreasing dosing frequency and toxicity. Thus, microencapsulation technology continues to be of much interest in controlled release-based partly on relative ease of design and formulation and partly on the advantages of microparticulate delivery systems [5]. Microencapsulation also protect drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein [6-7]. Microencapsulated pharmaceutical products have an active drug know as the core material surrounded by a shell known as the coating material or embedded into a matrix structure. Commercially available microcapsules contained 10-90 % w/w core. The realization of the potential that microencapsulation technology involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microencapsulation methods [3].

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

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- 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[8,9].

Solvent evaporation technique to formulate microcapsules of pharmaceuticals:

Solvent evaporation technique for microencapsulation of pharmaceuticals involves four major steps, like incorporation of pharmaceuticals, droplet formation, solvent removal, and drying.

Incorporation of pharmaceuticals:

The polymer is dissolved in a suitable water immiscible solvent, and the pharmaceutical agent is directly added into the solution of polymeric-matrix materials by dissolution/dispersion in suitable solvents, or emulsification of aqueous solution of the pharmaceutical agents immiscible with the matrix-material solution. For the preparation of solution or dispersion of pharmaceutical agents, impeller or static mixing, high speed-stator mixing or microfluidization techniques are generally used.

Droplet formation:

This step determines the size of resulting microcapsules. The size of microcapsules affects the drug encapsulation efficiency and the rate of drug release. The following procedures are used in droplet formation, namely:

Stirring:

The external phase is filled into a vessel and 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 [10].

Static mixing:

Static mixer consists 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 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*:*

Microcapsules have been prepared by dripping 10 % and 15 % (w/w) solution of poly (ethylene-co-acetate) in dichloromethane, containing dispersed protein particles from a needle into an electric field [11]. The droplet formed was dethatched from the needle by electrostatic forces.

Solvent removal*:*

Solvent removal can be achieved either by evaporation or by 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 can be performed, namely:

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 microcapsules.

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 microcapsules.

Microsphere Drying*:*

Solidified microparticles from the continuous phase are by either 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 microparticles are dried at elevated temperature or under reduced pressure to yield free flowing powder.

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. The system is agitated until the solvent separates into the aqueous phase and is

removed by evaporation. This process results in hardened microsphere, which contains drugs or agents to be encapsulated [12-16]. Usually, high shear is used to prepare emulsion; the resultant product has a much smaller particle size than the emulsion produced by conventional agitation. Other methods to prepare emulsion include the use of a microfluidizer and sonication. A major problem related with this technique is poor encapsulation efficiency of moderately water-soluble and water-soluble compounds, which partitioned out from the organic dispersed phase into the aqueous continuous phase. Successful entrapment of drug within microcapsules is thus highly dependent on its solubility in the aqueous phase.

Water-oil-water multiple emulsion followed by solvent evaporation system:

This method for preparation of microsphere was reported to overcome the problem of low encapsulation efficiency of water-soluble drugs prepared by conventional w/o emulsion solvent evaporation method [17,18]. In this technique, polymer is dissolved in a suitable organic phase. In this organic phase, aqueous drug solution is emulsified using high-speed homogenizer operating around 15000-20000 rpm for about 30 seconds to prepare w/o primary emulsion. This primary emulsion is added to external aqueous phase containing surfactant at homogenizer speed around 8000 rpm for 30 seconds and then stirred at 300 rpm for 3 hours at room temperature for permitting evaporation of organic solvent or it can be also performed under vacuum. The microcapsules obtained is collected by ultracentrifugation, filtration and then, lyophilized. Among them, lyophilisation decreases the burst effect. However, it may be change from drug to drug to obtain acceptable microcapsule size and drug release.

Water/oil/oil or water/oil/oil/oil multiple emulsion followed by solvent evaporation:

Iwata and McGinity developed a multiple emulsion of the W/O/O/O type [19]. Multiphase microcapsules of PLGA containing water-in oil (W/O) emulsions were 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 in this investigation. Drug loading efficiencies of model water-soluble compounds was found 80 to 100 %. Scanning electron microscopy of transverse cross sections of the multiphase microsphere of 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 denaturasation 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 [19, 20].

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 W1 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.

A study of process variables which influencing microencapsulation:

Effect of polymer*:* Various polymers have their inherent quality. Therefore, the quality of the microencapsulation varies depending upon the polymer used. In pharmaceutical industry, biodegradable polymers are used for microencapsulation. Polymers used for microencapsulation of pharmaceuticals are:

- Natural proteins like albumin, collagen, gelatin, fibrinogen, casein, fibrin, hayaluronic acid, *etc.*
- Natural polysaccharides like starch, dextrin, alginic acid, chitin, chitosan, *etc.*
- Semisynthetic polysaccharides like ethyl cellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, methyl cellulose, hydroxyl propyle ethylcellulose, *etc*.
- Synthetic polymers like poly (lactic acid), poly (lactic/glycolic acid), poly (_-hydroxybutyric acid), poly orthoester, poly alkyl cyanoarylate, various grades of Eudragit, *etc.*

Owing to the excellent biocompatibility property of the biodegradable polyesters poly (lactic acid) (PLA) and poly (lactic-co-glycolic acid) (PLGA), these are the most widely used biomaterials for the microencapsulation of therapeutics and antigens [21-22].

Effect of drug to polymer ratio:

The drug to polymer ratio can influence the quality of the microcapsules prepared by solvent evaporation technique. In an investigation by our research group, we found a significant increase in drug entrapment efficiency (%) of ethyl cellulose microparticles containing metformin HCl prepared by solvent-evaporation technique ($P < 0.05$) was observed with the decreasing drug-polymer ratio (increasing polymer content), when stirring speed and surfactant concentration were constant [23]. The increasing amount of polymer facilitated better coating onto the drug particles. Decreasing the drug-polymer ratio from 1 : 2 to 1 : 6 (increasing the ethyl cellulose content) in the preparation of these ethyl cellulose microparticles resulted in the formation of comparatively larger microparticles (145.89 ± 18.95 to 373.60 ± 23.52 µm). Again, we have found the retardation of the drug release rate depends on the drug-polymer ratio. As the ethyl cellulose content in the microparticles increased, the drug release rate from these microparticles was decreased due to increased thickness of the polymeric matrix. In an investigation on the poly (methyl methacrylate) (PMMA) microspheres loaded with bovine serum albumin (BSA), a ratio of less than 1:10 was suggested to yield protein loadings of > 80 % [24]. A higher load of bioactive material is likely to decrease the encapsulation efficiencies of proteins and peptides in PLGA [24- 25], and increase the drug release rate.

Effect of organic solvents*:*

Bodmeier and McGinity have performed an investigation on preparation of quinidine sulphate microsphere using o/w emulsion-solvent evaporation technique

to understand the effect of solvent, volume of solvent on drug loading. They have 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 [26]. 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 methylene chloride and the drug content was found to be higher in microspheres prepared with methylene chloride as

compared that with chloroform. This showed that the solubility of drug in solvent as an important factor, which was affecting entrapment of the drug content in the microcapsules. An important factor is the aqueous solubility of the organic solvent used for the microencapsulation using solvent diffusion. This helps the solvent removal from the water/air interface by evaporation. Methylene chloride has the highest aqueous solubility of the organic solvents forming microsphere as well as the lowest heat of evaporation. Solvent with very low aqueous solubility like benzene and chloroform diffused very slowly into the aqueous phase. The droplets were in the liquid state for a long period and drug could be easily diffuse across the non-precipitated droplet surface to aqueous phase resulted in to lower drug content [26]. The significance of solubility of the organic solvent in water was also confirmed by the fact that the addition of water miscible cosolvents 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 [27]. Secondly, water miscible solvent, methanol facilitated diffusion of water into dispersed phase.

Effect of drug solubility 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 [26].

Rate of solvent removal*:*

The rate of solvent removal from microsphere prepared by the solvent evaporation technique has a great impact on the physiochemical properties of the microsphere [28-29]. In an investigation, Izumikawa *et al*., [28] have 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 was 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 PLA. The RSE 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 favors denser to 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 [29] or albumin [30] in small (0.7-1.2µm) PLA microsphere. In both studies, poly vinyl pyrrolidone (PVP) solution was used as continuous phase. Evaporation of the solvent (here, dichloro methane) was accomplished within 6 hrs at 760 mm of Hg or 2 hrs at 460 or 160 mm of Hg at 25°C. In both cases, the drug encapsulation efficiency was decreased at reduced pressure whereas the drug release profile remained unaffected.

Effect of preparation temperature:

Yang *et al*., have studied the influence of preparation temperature on the various characteristics and release profile of PLGA microspheres, prepared using solvent evaporation technique [31]. They have studied the formation of PLGA microspheres in varying temperature (4-42°C). The PLGA microspheres tend to be larger when prepared at higher temperature (38 and 42°C), showed wider size distributions, and decreased particle density as compared to microsphere prepared at lower temperature (4- 33°C). The morphology of the particle interior (honeycomb-like) and drug encapsulation efficiency (53 % to 63 %) were unaffected by the preparation temperature. In case of PGLAPEG blend, drug 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, drug encapsulation efficiency was affected with a minimum efficiency of 15 % at 22°C, which steadily got improved (around 52 %) for lower and higher temperatures. Microspheres prepared at high temperature were found to be a uniform internal pore distribution and a very thin dense skin layer, 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. In term of *in vitro* drug release, microspheres fabricated at low temperature (5, 15, 22°C) exhibited similar steady drug release rates. However, microspheres formed at higher temperature exhibited low release rates after their initial drug release.

Effect of interaction between drug and polymer*:*

The interaction between drug encapsulated and polymer can change in drug encapsulation efficiency. The interaction between drug and polymer may be hydrophilic or hydrophobic interaction. In case of hydrophilic or ionic interaction, the drug is best encapsulated in polymers containing free carboxylic end groups. In case of hydrophobic interaction, relatively hydrophobic end capped polymers are more effective in increasing encapsulation efficiency [32]. On the other side, such interaction between drug and polymer may limit the protein release from the microsphere [33]. In certain cases, co-encapsulated excipients 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 [20].

Effect of buffer or added salt:

The buffer and salt added in the system can change the quality of the microencapsulation. In an investigation, Herrmann and Bodmeier have prepared somatostatin acetate-containing polylactide microspheres and evaluated these prepared microspheres for drug encapsulation efficiency, drug release, and morphological properties [34]. They have found that the addition of buffers and salts to the internal aqueous phase resulted

in the formation of a dense and homogenous polymer matrix. The drug release profile of these somatostatin acetate containing polylactide microspheres consisted of a rapid drug release phase followed by a slow release phase. Addition of buffer salts to the internal aqueous phase might be promoting 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 drug encapsulation efficiency. Al-Maaieh and Flanagan have found an increased drug loading in microspheres prepared using solvent evaporation technique by changing the aqueous solubility of both, the drug and the organic solvent [35].

Effect of internal aqueous phase volume on loading capacity*:*

Comparatively with large volume of internal aqueous phase (500 µl or 1000 µl), decrease in loading efficiency of ovalbumin was occurred [36-37]. While using smaller of internal phase of 50 µl, high drug loading efficiency was observed. With the increment of internal phase volume, thin layer of phase (methylene chloride) might be formed, which could act as a barrier for diffusion of drug to the external aqueous phase. With the thinner organic phase, the more diffusion and probability of diffusion from internal phase to external phase was observed, which could lower the drug loading efficiency. So, small internal phase volume was found to be beneficial to get high drug loading [38].

Effect of external aqueous phase volume on loading capacity:

Parikh *et al*., [37] have 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.

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 . In the investigation by our group, we found that increased stirring speed produced smaller sized microparticles using emulsification solvent evaporation technique. This phenomenon strongly supports the idea that the high stirring speed could provide high shearing force needed to breakdown the drug-polymer droplets into smaller particles [24]. The drug release from these smaller microparticles prepared with high stirring speed was found faster than that lower speed. The reduction of mean particle size of microparticles could facilitate higher rate of drug diffusion from larger surface area provided by the smaller microparticles.

Conclusion

The solvent evaporation method for production of PLA and PGLA microsphere has been used extensively for the encapsulation of a variety of pharmaceutical products. The efficacy of this microencapsulation process is dependent on various 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 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, new 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 capacity.

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Declaration of Interest:

It is hereby declared that this paper have any conflict of interest.

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