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REVIEW

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Solvent Evaporation Techniques as Promising Advancement in Microencapsulation

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ABSTRACT

In recent times solvent evaporation techniques have gained prominence in microencapsulation process. Solvent evaporation techniques are broadly classified into emulsification solvent-evaporation and extraction methods. Several variations have been developed recently based on this technology. Using solvent evaporation methods we can regulate microsphere morphology and other characteristics to the desired level for the targeted delivery of bioactives like peptides and vaccines using various biomaterials as carriers. Several methods of solvent evaporation, core and coat materials used, emulsion stabilizers, and process variables were discussed in detail with due interest of recent advancements in this area of research. This technology is showing a promising future for drug targeting and throwing challenges to pharmaceutical scientist such as: scale-up problems, use of non-organic solvents, use of alternative biodegradable polymers, and the application of a viable hybrid technology by amalgamating various techniques of microencapsulation to overcome the problems of peptide degradation during the process and stability of microspheres after the process.

INTRODUCTION

Proteins and peptides delivery in the form of controlled release creates new challenges to pharmaceutical scientist. Investigators and pharmacologists have been trying to develop delivery systems that allow the fate of a drug to be controlled and the optimal drug dosage to arrive at the site of action in the body by means of novel microparticulate dosage forms. During the past two decades, researchers have succeeded in part in controlling the drug-absorption process to sustain adequate and effective plasma drug levels over a prolonged period of time by designing controlled release microspheres intended for either oral or parenteral administration. Targeted or site-specific microparticulate delivery systems were also developed to alter the pharmacokinetic profiles of various therapeutic classes of drugs resulting in maintaining effective drug concentration for a prolonged period and result in decreased side effects associated with lower plasma concentrations in the peripheral blood without attempting to modify the normal buffet of the active molecules in the body after administration and absorption.

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Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 μm. They are made of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include gelatin and albumin whereas the synthetic polymers include polylactic acid and polyglycolic acid [1-4]. The influence of hydrophilic protective colloids was studied by Lin *et al.* [5].

Microencapsulation is a process by which a drug substance is entrapped within discrete free-flowing polymeric particle microcapsule products [6-16]. Different types of coated particles can be obtained depending on coating process used. The particles can be embedded within a polymeric or proteinic matrix network in either a solid aggregated state or a molecular dispersion, resulting in the formulation of micromatrices. Alternatively, the particles can be coated by a solidified

polymeric or proteinic envelope, leading to the formation of microcapsules.

A large number of microencapsulation processes and modifications of processes have been reported in the literature and in various patents, offering a variety of opportunities for the pharmaceutical technologist to choose from [17]. Crainich Jr has stressed upon the need to develop better scale-up technologies for microencapsulation processes [18]. Solvent evaporation technique has been successful in recent years for the preparation of microspheres in various applications and showing a promising future for its advantages over other techniques. Using this technique, controlled delivery of peptide drugs and vaccines has become realistic today in the form of micro- and nanospheres [19-22]. Thus solvent-evaporation technique does pave a way for identifying a better share in microencapsulation technology. The solvent evaporation technique and characteristics of biodegradable polylactic acid and poly(lactic-co-glycolic) acid (poly-DL-lactic acid-co-glycolic acid) microspheres produced by this method is presented by O'Donnell and McGinity [23, 24]. In this article we review the method of solvent evaporation covering the techniques and variations involved, core and coat materials used, process variables, problems involved and prospective scope of the method extending the coverage to all polymers along with biodegradable polymers.

Solvent evaporation technique

Way back in 1933 Hickey *et al.* prepared microcapsules using this technique. But the solvent evaporation technique was fully developed in 1979 [25, 26]. This technique is based on the evaporation of the internal phase of an emulsion by agitation. Generally, the polymeric coat material is dissolved in a volatile organic solvent. The drug core is then dissolved or dispersed in the above polymer solution to form a suspension, an emulsion or a solution. Then the organic phase is emulsified under agitation in a dispersing phase consisting of a nonsolvent of the polymer, which is immiscible with the organic solvent, which contains an appropriate emulsifying agent. Once the emulsion is stabilized, agitation is maintained and the solvent evaporates after diffusing through the continuous phase resulting in solid microspheres. The microspheres are recovered by filtration or centrifugation and are washed and dried (Fig.1) [27]. Several researchers have prepared microspheres of various bioactive materials using this technique and its variants.

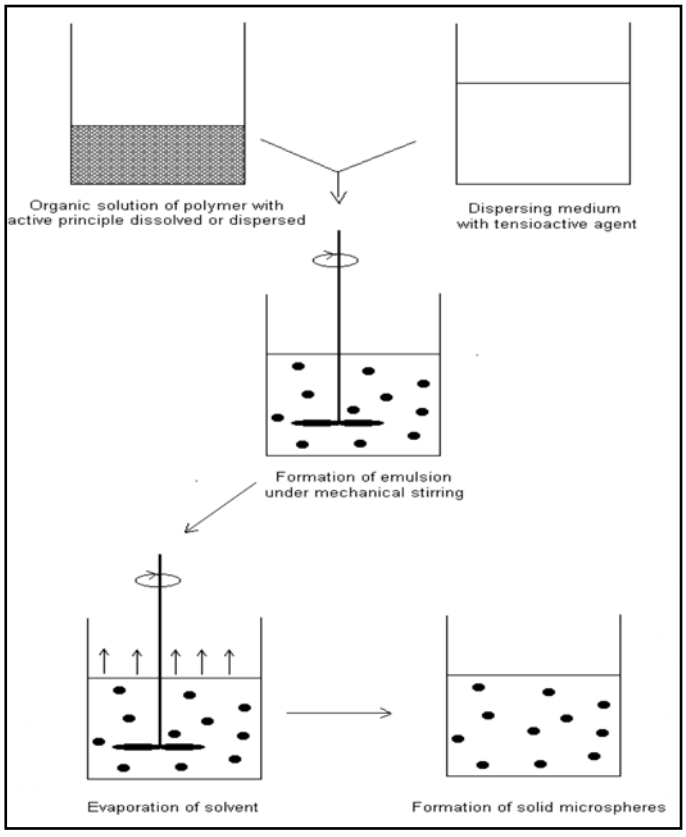

Figure1: The principle of the preparation of microspheres following the solvent evaporation technique.

Although the concept of the solvent evaporation technique is relatively simple, the physicochemical parameters governing this process are very complex. This system is characterized by the existence of several interfaces through which mass transfer occurs during particle formation [28, 29]. Mathematical models based on mass transfer were derived and used to predict microsphere properties prepared using solvent evaporation/ extraction methods (Fig. 2) [30]. The formation of solid microspheres is brought about by the evaporation of the volume of solvent L1 at interface L2/G. During the course of solvent evaporation, a partitioning is produced across the interface L1/ L2 from the dispersed phase to the continuous phase leading to the formation of solid microspheres. The partitioning across the interface L1/L2 is, however, not limited to organic solvent; the active principle may also partition to some extent at this interface. The rapidity and importance of these different transfer processes have a direct effect on microparticle formation. The rate of evaporation can be modified by rapid dilution of external phase, raising the temperature of external phase [31, 32]. Another way is by extracting the solvent using a common solvent for both internal and external phases. Thus, by studying the various governing parameters, the establishment of optimal conditions for the formulation of individual polymer/drug can be achieved.

The solvent evaporation method has attracted the most attention because of its ease of use and scale-up and lower residual solvent potential compared to other processes.

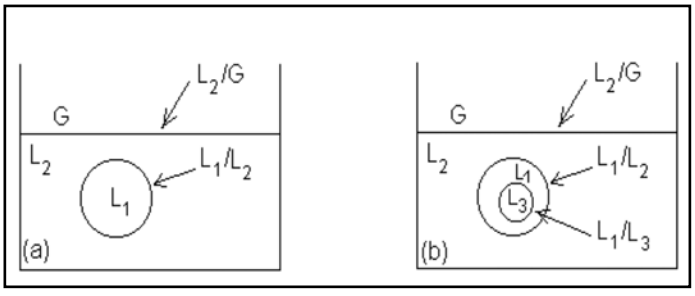

Figure 2: Schematic representation of the different interfaces in the solvent evaporation process: (a) simple emulsion; (b) multiple emulsion.

The systems of solvent evaporation method can be based on;

(a) the nature of the external phase either aqueous or non aqueous;
(b) the incorporated mode of the core material in the organic solution of the polymer either dissolved, dispersed or emulsified; and
(c) the elimination procedure of the organic solvent by either evaporation or extraction.

Classification of solvent evaporation technique

The classification proposed by Aftabrouchad and Doelker is applicable to microspheres prepared using solvent evaporation technique [33].

A. Solvent Evaporation (Emulsification-Evaporation):
   1. Oil-in-Water Emulsion (o/w)
   2. Multiple Emulsions: Water-in-Oil-in-Water (w/o/w)
   3. Nonaqueous Emulsions
B. Solvent Extraction (Emulsification-Extraction)

A: Solvent evaporation (emulsification-evaporation)

A1: Oil-in-water emulsion (o/w): In this technique water acts as a non-solvent to the polymer. This method is also known as "in-water drying" developed for encapsulation of water-insoluble drugs and its use with polylactide polymers was reviewed in detail [34-37]. This process is very economical and eliminates recycling of an external phase [38-40]. In this system, the polymer is dissolved in an organic solvent such as methylene chloride or chloroform. The drug is dissolved or dispersed in the same medium and then entire mixture is emulsified in an aqueous solution containing an appropriate surfactant. Beck *et al*. were the first to propose this procedure for the encapsulation of progesterone in poly (D,L-lactic acid) (PLA) microparticles [26]. Nanospheres were also prepared using same technique [41]. The residual organic solvent is usually removed under reduced pressure. The emulsifier can be removed by dialysis of the suspension or by washings following the separation of free particles by filtration or ultra centrifugation. This technique is mostly useful for several lipophilic drugs. This procedure was applied to the encapsulation of a few water-insoluble peptides such as salmon calcitonin and cyclosporine [30, 42-44]. A rise in temperature for solvent evaporation causes formation of large core and thin polymer coat and the dilution technique produced porous microcapsules.

The physicochemical characteristics of the core materials like partition coefficient, degree of ionization will decide the entrapment efficiency of the microspheres formed. Water-soluble drugs cannot be encapsulated efficiently in the o/w system because they partition out into the external phase resulting in negligible entrapment in the microspheres. The drug should be made soluble in the polymer solution (oil phase). The solvation of core substance in organic solutions of polymers can be enhanced by the addition of hydrophilic cosolvents [45-47]. Conversion of hydrophilic drugs such as floxuridine to lipophilic drugs is another way to increase microencapsulation yields [48]. Loss of active ingredient from oily dispersed phase to aqueous continuous phase can also be reduced by saturating the continuous phase with the drug substance which is less water soluble, adjusting the pH of same phase provided there is no degradation of polymers or even adding electrolytes [34, 49-52]. The pH sensitive polymers such as eudragits and cellulose acetate butyrate (CAB) were employed for preparation of microspheres for oral delivery [53-55]. Recently the mechanisms of burst release from pH-responsive polymeric microparticles using this technique was studied [56]. Mucoadhesive microspheres can be formulated using CAB and dextran derivatives [57]. Floating microspheres were also prepared using this technique [58, 59].

A2: Multiple emulsions (Water-in-oil-in-water or w/o/w): This procedure was first patented by Vrancken and Claeys in 1970 and further by DeJaeger and Tavermier in 1971 [60, 61]. Typically, an aqueous solution of the active principle was poured into an organic solution of the polymer to form an emulsion of the type water-in-oil (w/o). This primary emulsion is itself emulsified in an external aqueous phase leading to a multiple emulsion of the type water-in-oil-in-water (w/o/w). This procedure was further modified to enhance encapsulation of highly water-soluble peptides and anaesthetics [8, 62, 63]. Several authors have reviewed about biodegradable microspheres for peptide delivery using this technique [29, 64-66]. This process is very useful for the encapsulation of drugs in weak doses, which are strongly water soluble like hormones and trophic factors and antigens [13, 14, 67-75].

Various modes of mixing have been used for primary emulsification including high-speed homogenization, microfluidization, probe sonication, vortexing and static mixers. High-speed homogenization is by far the most popular method because of the different configurations of rotors, stators and their combination available, the ease of scale-up when compared to other procedures. As the homogenization speed increases in rotor-stator homogenization the droplet size decreases until an equilibrium droplet size is achieved whereas the homogenization time does not affect much on the equilibrium droplet size [76]. Drug loading and encapsulation efficiency decrease and drug release rate increases with high-pressure homogenization during the emulsification process [77]. The high-pressure emulsifier is produced by Microfluidics [18]. This equipment can emulsify oil droplets down to particle size of 400 nm. This process can achieve the microsphere size suitable for injection through a normal 22-23 gauge needle. Biodegradable polymeric drug carriers to pass across blood-brain barrier have been prepared using high-pressure emulsification process [78]. The organic phase acts as a barrier between the two aqueous compartments preventing the diffusion of the drug substance toward the external phase [40].

The viscosity of the primary emulsion influences the entrapment of the drug, the particle size and morphology [79]. The role of viscosity of the primary emulsion (w/o) in the prevention of the diffusion of the active principle toward the external aqueous phase was studied by Ogawa *et al*. [8]. The viscosity can be increased by increasing the polymer concentration in the organic solvent, addition of drug retaining

substance, lowering of temperature and adjusting the ratio of internal aqueous phase to the polymer-organic solution phase. Viscosity increasing agents like gelatin, pectin and agarose could prevent the diffusion of active principle but at the same time they were found to be incompatible with active principles.

The United States Food and Drug Administration (USFDA) has drawn certain standards about the following parameters of microspheres for parenteral depot administration [80]. These are: polymer/copolymer, organic solvents, copolymer-peptide complexes, sterilization, *in vitro in vivo* correlations, particle size and diluent-suspending vehicle. The first FDA approved system for controlled delivery of a peptide was an injectable poly(lactide-coglycolide) microsphere formulation of leuprolide acetate. Commercially it is available with brand name Lupron Depot. In France, it was marketed under the name of Enantone LP and is prescribed in the treatment of prostate cancer along with Décapeptyl L.P. Another drug, goserelin acetate is being sold as Zoldex by I.C.I.

A3: Influence of process variables

The sphericity, size and yields of the microspheres are influenced by several process variables like nature of solvent, polymer concentration, emulsifier type and concentration, phase volume ratio, temperature and drug to polymer ratio [81, 82]. Influence of process parameters was also investigated and optimized [83-85].

The selection of solvent and external continuous phase determines the microsphere formation and entrapment efficiencies. The solvent properties should include:

- good solvency for the polymer for better drug entrapment,
- poor solvency for the drug to minimize partitioning of the drug into external phase,
- low boiling point for easy evaporation,
- immiscibility with continuous phase yet should have a finite solubility with it for solvent evaporation to occur,
- does not cause the degradation of the dug substance, and
- acceptable for human use.

Methylene chloride is most widely used solvent in microencapsulation technique. It suffers from the drawback of being carcinogenic and has a low solubility in water [65]. Other solvents with a lower toxicity than methylene chloride, such as ethyl acetate have also been used in microencapsulation. Ethyl acetate suffers from the disadvantage of being a poor solubilizer for higher molecular weight polymers and those with a monomer ratio of 50:50 mole % (lactide:glycolide) [86].

The external phase should be high boiling, non-toxic, immiscible with the organic solvent used and less expensive. Water is the only medium that fulfills all these requirements. Other vehicles like vegetable oils, mineral oils, organic solvents, etc., have also been used to enhance entrapment efficiencies but they suffer from the disadvantage of residual levels in the finished product [87]. Ethylcellulose microspheres of aspirin were prepared avoiding surfactant and using non-toxic solvents [88].

A good emulsifier is required for the stabilization of an external phase to prevent the formation of agglomerates of microspheres during an early evaporation stage. As the evaporation proceeds, the emulsifier film helps to maintain the spherical shape of droplets till such time as the droplets are hardened enough to be harvested. The surfactant such as albumin or polyoxyether-polyoxypropylene copolymers is employed for the stabilization of primary emulsion. But one problem persists as the primary surfactant could leach out into the external aqueous phase during secondary emulsification along with the diffusion of the internal water and organic solvent during solvent evaporation. This would probably generate a microsphere matrix that is more porous and would result in a large burst effect and a drug release via a diffusion process rather than through the process of degradation of the polymer. Lipophilic surfactants do not much affect on the physical characteristics of microcapsules but particle charge depends on the concentration and type of the surfactant used [89]. By selecting the appropriate HLB value of emulsifier can control the encapsulation efficiency, size and morphology of microspheres [90]. The emulsifiers that have been used include polyvinyl alcohol (PVA), poly (vinylpyrrolidone) (PVP), polysorbate 80, gelatin, alginate, methylcellulose, polysorbates, hydroxypropyl methylcellulose, sodium lauryl sulfate, etc. [87, 91]. Poloxamer 407 and poloxamine 908 were also used as surfactants to prepare poly(DL-lactide-coglycolide (polyglactin 370) nanospheres [92]. Carbopol and poloxamer were employed and found to be alternatives to polyvinyl alcohol as emulsion stabilizers [77, 93].

Polyethylene glycol (PEG)-dextran conjugates were used as combined stabilizer and surface modifier to produce PLG microparticles that have a mean particle size of 480 nm [94]. The major problem associated with the use of polymeric microspheres, their natural surface characteristics favor protein binding and thereby phagocytosed due to opsonization. PEG conjugates of hydrophobic drugs allow surface modification of biomaterials that does not favor microspheres for protein binding and hence they are not phagocytosed. This technology has been commercialized by Nottingham Technology Ventures. The effect of different surfactants on entrapment and drug release was studied using a peptide pBC-264 from polyglactin 370 microspheres resulting in reduced drug loading into microspheres and increased burst release [95]. Smoothing agents like aluminium tristearate and polyisobutylene can be employed to yield very smooth microspheres [96, 97]. Mechanism of elimination of solvent influences the microparticle morphology [98].

The use of drug retaining substances such as gelatin, albumin, pectin, etc., in the inner aqueous phase aids in achieving higher drug loading through an increased viscosity of inner aqueous phase. A reduction in the temperature of the primary emulsion aids in enhancing the entrapment ratio of the drug. But, as the overall viscosity of the primary emulsion increases the particle size also increases where above a certain viscosity the particles are actually deformed upon secondary emulsification [62].

Temperature also influences emulsion-stabilizer incorporation [99]. Solidification time influences the final particle size of microspheres [100].

Several biomaterials were tried to prepare microspheres using this technique several of them are biodegradable. Low molecular weight polyesters; PLA, PLGA and PV (poly delta-valerolactone) are more effective for parenteral drug delivery [101]. PLGA microcapsules sterilized by gamma irradiation are stable [102]. Vandervoort and Ludwig studied the effect of drug-polymer ratio on drug entrapment using w/o/w technique [103]. An increase in the concentration of the polymer in the organic solvent causes an increase in the viscosity of the polymer solution, the viscosity of the primary emulsion, the stability of the primary emulsion and also the rate at which the polymer precipitation occurs upon secondary emulsification. This results in higher entrapment efficiency upon secondary emulsification [65]. Effect of primary emulsion stability was also studied by Nihant *et al*. Microsphere morphology and porosity are influenced by emulsion stability [104, 105]. An attempt was made to reduce the toxicity of cyanoacrylate polymer by PEGylation and has shown reduced toxicity of the polymer towards mouse peritoneal macrophages. This also increased biodegradability of the polymer in the calf serum, which is essential for parenteral controlled delivery of drugs [106]. The nature of polymer also plays an important role in particle characteristics. The effect of the molecular structure of hydrophobic polymers on their interfacial activity at the methylene chloride-water interface, as well as on the emulsifying ability and the size of nanoparticles obtained by emulsification-solvent evaporation, has been studied [107]. A blend of polymers such as PLA and PLGA, can be used to obtain microspheres having desired release rate profiles [108]. In another study poly (D, L-lactide) was employed for vaccine delivery [71]. When polymer combinations were used other factors such as structural effects must be considered [109]. Polymer blends may alter the net glass transition temperature and thus influence the drug release from the microspheres [110]. The molecular weight of the polymer also influences the microsphere characteristics and drug release properties from microspheres [111, 112]. Microspheres for lysozyme delivery were prepared from hydrophilic poly(ethylene glycol) (PEG) blocks and hydrophobic poly(butylenes terephthalate) (PBT) resulting in perfectly spherical microspheres [113]. The stability of lysozyme was found to be good in poly(ethylene glycol terephthalate)-poly(butylenes terephthalate) (PEGT/PBT) [114]. In a recent study a novel emulsification technique assisted with amphiphilic block copolymers was developed for PEG-PLA/PLGA microparticles for pulmonary drug delivery [115].

The increase in the phase volume ratio between internal aqueous phase to the oil phase results in insufficient availability of polymer for entrapment of internal aqueous droplets. This results in the loss of the drug as well as internal water from the microsphere matrix into external aqueous phase during secondary emulsification stage and creates a microsphere system with a high porosity through which the drug substance is released at a faster rate [15].

The pH of internal aqueous phase determined the state of ionization and thereby interaction of the polymer and the drug substance. Such an interaction is beneficial to enhance entrapment, to reduce the burst effect and to control the release rate of the drugs. This phenomenon was demonstrated for the encapsulation of somatostatin acetate within PLA microspheres and for leuprolide acetate and thyrotropin within PLGA microspheres [15, 62]. The drug-polymer interaction may also result in degradation of drug or poor release profiles [86]. Use of additives such as $NaHCO_3$ and sucrose can enhance the entrapment efficiency and stability of microcapsules [116].

Recovery of the microspheres is done by filtration or centrifugation. Drying of the wet microspheres is usually done by lyophilization process for peptide drugs. Other techniques like rising of the temperature of the product above the glass transition temperature of the polymer results in the agglomeration of the microspheres. So a careful control on the drying conditions is essential to achieve a product of reproducible quality. Freeze drying can be employed on embryonic microspheres to achieve the increased extent of burst release [117].

A3: Nonaqueous Emulsions: In this technique both the continuous and dispersed phases are oily in nature but are immiscible with each other. The continuous phase is usually a mineral or vegetable oil or a non-volatile organic solvent [34-37]. This technique has only been used for the encapsulation of a very limited number of drugs including cytostatics, antiinflammatories, antimalarials, anxiolytics and serum albumin [45, 54, 81, 118-127]. This process can be utilized to provide a protective barrier between the drug and the polymer-solvent phase and to prevent the highly water soluble drugs from partitioning out of the microspheres. Lamivudine and stavudine microcapsules were prepared and characterized us by using acetone as solvent and liquid paraffin as dispersion medium [128, 129]. A variation of this technique consists of replacing the solvent evaporation by sublimation process through lyophilization after emulsification step resulting in porous microspheres [130]. A multiunit floating drug delivery system of rosiglitazone maleate has been developed by encapsulating into Eudragit RS100 through this method [131]. This process gives increased entrapment of water-soluble drugs; help prevent the eventual hydrolysis of drug or polymer. But, compared with aqueous emulsions, this technique exhibits a number of disadvantages related to the use of non-aqueous solvents that may be costly and the residual solvents are difficult to eliminate from microspheres [132].

B: Solvent extraction (emulsification-extraction)

The evaporation stage in the solvent evaporation process can be avoided by using large volumes of dispersing phase with respect to dispersed phase or by choosing a dispersed phase consisting of cosolvents, of which at least one has great affinity for dispersing phase, which acts as solvent extractor [71, 72, 133]. This technique was employed to prepare microspheres of albumin and naproxen [134-136]. Solvent extraction process could be

advantageous compared to solvent evaporation and spray drying processes resulting in particles that are more regular in shape, smaller with narrow size distribution and high porosity [137].

New modifications of solvent evaporation techniques

Several innovative modifications of emulsification solvent evaporation/extraction techniques have been developed, including water-in-oil-in-water-in-oil (w/o/w/o), water-in-oil-in-oil (w/o/o), water-in-oil-in-oil-in-oil (w/o/o/o) and solid-in-oil-in-water (s/o/w), water-in-oil (w/o), thus widening the scope of these techniques [23, 88, 114, 135, 138-143].

A hybrid technology may be employed where emulsification-evaporation is initialized then interrupted before the volatile solvent is totally eliminated. This is done by transferring the microspheres into a large volume of continuous phase where the remaining solvent is eliminated by extraction [144]. This technique was used for the prevention of crystal formation of the drug on the microspheres during solvent evaporation stage [145, 146]. A very interesting alteration of this technology involves injection of a polymeric support solution containing the drug in a solvent-extracting medium. The entire mixture is placed in a tubular system with reservoirs designed to permit the total extraction of the solvent from the polymer. This system replaces the mechanical stirring process and can be used for the production of microspheres on a continual basis [147]. Another variation in solvent evaporation/extraction techniques is the use of membrane emulsification technique in which microporous glass membranes are used for preparing monodisperse microspheres [83, 148]. Buoyant hollow microspheres can be prepared by dissolving carbon dioxide gas under pressure into the drug-polymer dispersions. Upon the release of the pressure, the gas bubbles are formed and entrapped in the dispersed drug-polymer droplets and eventually formed internal cavities in the microspheres [59]. Supercritical (SC) fluid technology can be employed to achieve desired porous properties to microspheres. In another method SC CO2 pressure-quench treatment was applied to prepare large porous deslorelin-PLGA particles with reduced residual solvent content, which retained deslorelin integrity, sustained deslorelin release, and reduced cellular uptake [149]. An interesting novel concept was developed for the continuous, contact- and contamination-free treatment of fluid mixtures with ultrasound. It is based on exciting a steel jacket with an ultrasonic transducer, which transmitted the sound waves via pressurised water to a glass tube installed inside the jacket. This avoids the release of metallic particles and contamination of fluid from environment making the method highly suitable for aseptic production of microspheres [150]. The summary of research works involving solvent evaporation techniques using several core and coat materials is shown in the Table 1.

Conclusion

Microencapsulation of various bioactive materials is a challenging field for research especially for peptide or protein drugs. Solvent evaporation technique has been a better choice for the microencapsulation process to get desired product characteristics in recent times especially for peptide and vaccine delivery. It can be observed from the above discussion that a variety of factors are responsible for achieving the correct microsphere characteristics of particle size, entrapment efficiency and drug release. Certain regulatory concerns like residual solvent and emulsifiers, sterility and syringeability have become prime importance today. The major challenges facing the pharmaceutical scientists include, scale-up problems, use of alternative solvents to replace methylene chloride, use of alternative biodegradable polymers to the polylactides/glycosides, application of hybrid technology for encapsulation of high molecular weight proteins, to overcome the problems of peptide degradation during the process and stability of microspheres after the process. The focus of research should be positioned on the above aspects resulting in a new variety of microspheres in the market with improved stability and therapeutic efficacy in the coming years.

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Table 1: Various active ingredients and biomaterials used for microsphere preparation using several solvent evaporation techniques.

Technique	Biomaterial	Active ingredient	Parameters studied	Ref
A	Ethylcellulose	Aspirin	Characterization	[151]
A	Ethylcellulose	Zidovudine	Formulation variables	[152]
A	Ethylcellulose	Theophylline	Effect of magnetic and propeller stirring	[153]
A	Ethylcellulose	Naproxen	Effect of polyisobutylene as protective colloid	[97]
A	Ethylcellulose, Carbapol	Clarithromycin	Characterization	[154]
A	Chitosan	Cyclosporine A	Characterization, bioadhesion	[155]
A	Chitosan	Lactoferrin	Characterization	[156]
A	Chitosan 2-iminothiolane conjugate	Fluorescein-isothiocyanate labelled dextran	Characterization, mucoadhesion	[157]
A	Poly (ε-caprolactone)	Propolis	Characterization	[158]
A	Poly (ε-caprolactone)	Isoniazid	Characterization	[159]
A	PLA, PLGA	Rotavirus (strain SA11)	Characterization	[160]
A	PLA	Naltrexone	Effect of surfactant HLB	[90]
A	PLG	Haloperidol	Characterization	[161]
A	PLA, PLGA	Estradiol	Characterization	[111]
A	PLGA	Chondrocyte	Surface modification	[162]
A	PLGA	Tamoxifen citrate	Charcterization	[163]
A	Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)	Rifampicin	Characterization	[164]
A	Poly (ortho ester) polymers	5-Fluorouracil	Process parameters	[123]
A	Eudragit RL-100 and Eudragit RS-100	Tolmetin	Polymorphic change of drug during process	[165]
A	Eudragit RS	Terbutaline sulfate	Characterization	[96]
A	Eudragit RS-100	Isoniazid	Characterization	[166]
A	Eudragit RS	5-Amino salicylic acid	Effect of surfactants	[167]
A	Eudragit L100, cellulose acetate phthalate, and hydroxyl propyl methyl cellulose phthalate	Pancreatin	Characterization	[168]
A	Eudragit RLPM	Nifedipine HPMC-MCC solid dispersions	Characterization	[169]
A	Eudragit RS-100, Eudragit RL-100 or ethylcellulose	Bromhexine hydrochloride	Characterization	[170]
A	Polystyrene	Indomethacin	Process variables	[171]
A	Cellulose acetate butyrate	Phenyltoloxamine citrate	Characterization	[172]
A	Cellulose acetate butyrate	Disopyramide	Characterization	[173]
A	poly[Lac(Glc-Leu)]	Valdecoxib	Characterization	[174]
A	Polyglactin 370		Characterization	[73]
A	Ethylcellulose, Cellulose acetate butyrate, poly (methyl methacrylate) and polylactide	Pseudoephedrine HCl	Characterization	[40]
A	Cellulose acetate butyrate	Terbutaline sulfate	Characterization	[175]
A	Cellulose acetate butyrate	Paracetamol	Characterization	[176]
A	Cellulose acetate butyrate, gelatin	Succinylsulphathiazole	Characterization	[177]
A	Ethyl cellulose, gelatin	Fluoride	Characterization	[178]
A	Polyglactin 370	Carmustin	Characterization	[179]
A	PLGA	Heparin	Characterization	[180]
B	Cellulose acetate phthalate, cellulose acetate butyrate, ethylcellulose, HPMCP	Lamivudine	Characterization	[128]
B	Cellulose acetate butyrate, ethylcellulose, HPMCP	Stavudine	Characterization	[129]
B	Chitosan-Thio –Butyl-amidine	Labeled Dextran	Characterization	[181]

A = o/w, B = w/o, C = o/o, D = s/o, E = w/o/w, F = w/o/o, G = w/o/o/o, H = w/o/w/o, I = s/o/w, J = solvent extraction and K = solvent evaporation extraction.

Table 1: Various active ingredients and biomaterials used for microsphere preparation using several solvent evaporation techniques.

B	PLGA, PLA	Cisplatin	Characterization	[182]
B	PLG	Pilocarpine	Process parameters	[77]
B	Ethylcellulose	Aspirin	Use of nontoxic solvents	[88]
B	Ethylcellulose	Isosorbide dinitrate	Characterization	[183]
B	Ethylcellulose	Ascorbic acid	Characterization	[184]
B	Cellulose acetate butyrate	Chlorpheniramine maleate-resin complexes	Effect of process variables	[185]
B	Chitosan	Oxantrazole	Statistical central composite optimization for characterization	[186]
C	Ethylcellulose, Cellulose Acetate and Eudragit RS100	Indomethacin	Comparative Evaluation	[187]
C	Cellulose acetate butyrate	Diclofenac sodium	Characterization	[54]
C	PLLA	5 FU	Characterization	[188]
C	Polyesters	Diclofenac	Degradation studies on polymers	[101]
C	Resomers	Diazepam	Monomer release determination by HPLC	[125]
C	Polyglactin 370	Cisplatin	Effect of variables	[121]
D	TAK-029	GPIIB/IIIa antagonist	Characterization	[189]
E	PLGA	Insulin microcrystals	Characterization	[190]
E	PLA/PLGA	Melittin	Characterization	[191]
E	PLA	rhI	Process parameters	[83]
E	High and Low PLGA	Pentamidine	Influence of Blends of polymers	[110]
E	PEGT/PBT	Lysozyme	Encapsulation in the films; microspheres Characterization	[113, 114]
E	Hydroxypropyl methylcellulose acetate	Bovine insulin	Characterization	[192]
E	Polyglactin 370	Hepatitis-B antigen	Characterization	[193]
E	Polylactic acid	Bovine insulin	Characterization	[194]
E	PLG	Isoniazid, Rifampicin	Characterization	[195]
E	Polyglactin 370	Peptide (pBC-264)	Effect of nature of surfactant, pH	[96, 196]
E	Polyglactin 370	Bovine albumin	Characterization	[197]
E	Cellulose acetate butyrate	Sulfadiazine	Effect of different surfactants	[198]
E	Polyesters	Somatostatin	Modified method	[15]
E	Polyglactin 370	V3-BRU peptide	Characterization	[199]
E	Polyglactin 370	Ovalbumin	Characterization	[73]
E	PLGA	Bovine serum albumin	Charcterization	[13]
E	Polyglactin 370	Ceftiofur HCl and Ceftiofur sodium	Cosolvent and dispersion methods	[47]
F	PLGA/ Polyanhydride	a-Cobrotoxin	Characterization	[200]
F	Polyglactin 370, poly(ethylene oxide) and poly (propylene oxide) copolymers	Ovalbumin	Characterization	[139]
F	PEG 8000, polyglactin 370	Ovalbumin	Characterization	[135]
G	PLGA	Thioridazine HCl	Characterization	[23]
H	Polyglactin 370	Ovalbumin	Characterization	[138]
I	PLGA	IgG	Characterization	[142]
I	PLGA	Tumor necrosis factor	Selection of solvent	[141]
J	PLGA	Bovine albumin-gelatin	Characterization	[134]
J	Polyglactin 370 and PEG 8000	Ovalbumin	Improvement of drug loading	[135]
K	A-PLGA	Huperzine	Formulation factors	[84]
K	Polyorgano-phosphazenes	Naproxen	Characterization	[136]
K	PLGA	Highly water soluble drug	Reduction in burst release	[201]

A = o/w, B = w/o, C = o/o, D = s/o, E = w/o/w, F = w/o/o, G = w/o/o/o, H = w/o/w/o, I = s/o/w, J = solvent extraction and K = solvent evaporation extraction.

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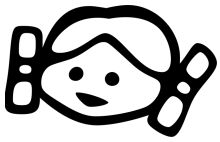

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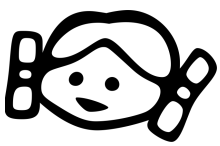

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