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Solvent Emulsification Evaporation and Solvent Emulsification Diffusion Techniques for Nanoparticles

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Abstract

Nowadays, there has been an increased demand of nanoparticulate-based drug delivery as nanoparticles (NPs) generally give more advantages over the conventional drug carriers for targeting in various parameters like more drug encapsulation, more stability and site specificity, sustained release profile and the ability to deliver both lyophilic and lyophobic types of drug particles using different modes of administration. Nanocarriers have been expansively studied as particulate drug delivery in the field of pharmaceuticals, due to their controlled and sustained release properties, small size and biocompatibility with body tissues. Manufacturing technique used to prepare nanoparticles plays a vital role in achieving their desired properties for a particular application. Several methods to formulate nanoparticles have been developed during the last many decades, and these are classified based on whether the particle formation undergoes a polymerization reaction or a nanoparticle forms directly from a preformed polymer or ionic gelation method. The choice of method for the preparation of nanoparticle is highly dependent on the physicochemical properties of both the polymer and the drug compound. Polymeric nanoparticles are generally manufactured by polymerization of monomers using anionic polymer or by preparing homogeneous dispersion of the dissolved polymers which gives nanoparticles using various methods such as solvent evaporation, emulsification solvent diffusion, salting out, emulsification diffusion and supercritical fluid (SCF) technology. This chapter emphasizes on how emulsification followed by solvent evaporation and solvent diffusion permits an emulsion of a polymer solution to customize as nanoparticles. The chapter also provides concise information on recent trends of research in specified domain.

Keywords

Nanoparticles · Emulsification solvent evaporation · Emulsification solvent diffusion

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1 Introduction

Current advances in drug development research arise from the multidisciplinary research by association of scientists from various fields such as chemistry, biology, pharmacology, medicine and engineering. Similar to such research for new active substances, controlled drug delivery technology represents one of the front-line areas of science, which also involves multidisciplinary scientific approach (Patil 2016). In particular, the involvement of nanoscience and physical chemistry of colloids seems very decisive, but the concepts proposed in nanotechnology have been executed to the profound limitation of the pharmaceutical applications. Much focus has been given to novel modes of drug administration because the most commonly used pills, tablets and parenteral solution were inadequate for many active pharmaceutical ingredients. The technological advances in nanotechnology make it more technical and accurate with a touch of interdisciplinary effect (Ahmad et al. 2012). Polymeric nanoparticles are defined as submicron (1–1000 nm) colloidal particles comprising active pharmaceutical ingredients encapsulated within or adsorbed to macromolecular polymer system (Chang 1992). The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Nanoparticles, nanospheres or nanocapsules can be obtained depending upon the use of manufacturing technique. Nanoparticles are carriers in which the drug is enclosed by a suitable polymeric membrane, whereas nanospheres are matrix carrier in which the drug is distributed homogenously as matrix (Catarina et al. 2006). Many types of drug delivery systems, namely, emulsions, gels, aqueous suspensions of microgel particles, liposomes and solid lipid particles, have been widely investigated. Polymeric colloidal carriers made of biocompatible polymers offer many technical advantages in terms of stability, processability and versatility for various applications (Domenico et al. 2019). These kind of delivery systems present numerous benefits to the physician and the patient compared to conventional dosage forms, which mainly include reduced toxicity, enhanced stability of the active substance, more encapsulation of drug and slow delivery rates that allow spacing out the doses or reducing concentration of active substance in the formulation; these advantages result in improved efficacy with decreased side effects, patient compliance and convenience (Brannon-Peppas and Blanchette 2004). These are the reasons why polymeric particulate carriers are most widely used in drug delivery technology. Passive and active drug targeting can be achieved by controlling particle magnitude including size and surface properties. Nanoparticles offer some specific advantages to increase the stability of active pharmaceutical ingredient (API) and retain useful modified release characteristics. The benefits of nanoparticles as a nanocarrier include (Mohanraj and Chen 2006) enhanced therapeutic value and reduced toxic effects; controlled or sustained release of drug; high drug loading; achievement of site-specific targeting by developing magnetic nanoparticle; suitable for various routes including ocular, oral, nasal and parenteral; and because of larger surface area, rapid dissolution of drug in body fluids, such as the human body with rapid absorption and more bioavailability.

2 Commonly Used Polymers for Nanoparticles

The general polymers used to manufacture nanoparticles should be biodegradable, biocompatible and non-toxic and should not give any type of antigenic effect (Yu et al. 2016).

2.1 Natural Polymers

The mostly natural-occurring polymers are used to prepare nanoparticles like albumin, chitosan, gelatin and sodium alginate.

2.2 Synthetic Polymers

Polyvinyl alcohol (PVA), polylactides, poly(lactic-co-glycolic acid) (PLGA), polygly-

colides, polyacrylic acid, polyacrylamide, polyglutamic acid, polymalic acid, polymethyl methacrylate, polyethylene glycol and polymethacrylic acid are some the commonly used synthetic polymers.

3 Mechanisms of Drug Release from Nanoparticles

The overall performance of nanoparticle is governed by capacity of a nanoparticle to release encapsulated drug. The polymeric nanoparticles release the drug when it reaches the targeted site by following the three mechanisms: (1) diffusion of drug molecule due to the swelling of the polymer nanoparticles by hydration, (2) rupture of the polymer at site of action by an enzymatic action resulting in releasing the drug from the encapsulated inner core and (3) desorption of surface adhered drug at the targeted site from the hydrated and swelled nanoparticles (Gi-Ho et al. 2017). Various nanoparticle properties like particle size, charge on the surface and its shape handle critical roles in generating actual functional drug delivery system by various mechanisms.

3.1 Effect of Particle Size

Size of nanoparticle play vital role in cell interaction, degradation and elimination of nanoparticle. The main focus of controlling particle size is avoidance of reticuloendothelial system (RES) uptake for degradation. By avoiding RES circulation time, the bioavailability of nanoparticles can be increased (Couvreur et al. 1995). Desai et al. (1996) studied that nanoparticle uptake of an in situ rat intestinal loop model demonstrated 15- to 250-fold increase in cellular uptake of small size nanoparticle when compared with larger microparticles.

3.2 Effect of Particle Charge

Stability of nanoparticle can be influenced by presence of charge on the surface of nanocarriers. A highly charged system offers more gradation of repulsion force between similar particles. This generated repulsive force leads to stabilization of nanoparticles and prevents aggregation (Nagavarma et al. 2012). Nanoparticles formulated with more evidential surface charges have shown to be more stabilize nanoparticle and prevent its further aggregation.

3.3 Effect of Particle Shape

Particle shape has been identified as a new physical parameter which has exerted tremendous impact on cellular uptake and biodistribution. A recent study has identified that there is a lower uptake of nanoparticle by macrophages due to its oblate shape which favours more circulation in the blood. Afterwards, this enhances the residence of nanoparticles in the blood and increases their probabilities of attaining their target site. Besides macrophages, the nanoparticle shape also favours endocytosis by normal and cancer cells (Sahay et al. 2010).

4 Methods for Preparation of Nanoparticles

Nanocarriers can be produced from various materials like natural polymer including polysaccharides and proteins, as well as by using synthetic polymers. The choice of polymeric materials depends on critical factors like (a) size of nanoparticles, (b) drug properties like solubility and stability in water, (c) surface characteristics such as surface charge and penetrability, (d) ability of biodegradation with good biocompatibility and less toxicity and (e) expected drug release pattern (Pathak and Thassu 2009). Nanoparticles can be obtained either by polymerization reactions or by dispersion of preformed polymers, either natural or synthetic. From literature, it was found that emulsion polymerization is the most frequently used polymerization method to produce nanoparticles but is less used for the purpose of encapsulation and drug delivery. Studies have been carried out on polyalkyl cyanoacrylate

nanoparticles which are prepared by emulsion polymerization processes. Other techniques like nano-encapsulation techniques using preformed polymers are preferable due to the toxic effects of residual substance present after a polymerization reaction and also adverse reaction with drug (Tiwari et al. 2012). The knowledge of proper selection of the nanoparticle manufacturing methods is a key issue for the research scientist who is involved with drug delivery research and development. Some preparation methods have been specifically developed for the manufacturing of nanoparticles from natural macromolecules or preformed synthetic polymers due to their easy implementation and lower toxicity potential. Most novel and widely used methods to prepare polymeric nanoparticles are solvent emulsification diffusion process and solvent emulsification evaporation method.

4.1 Emulsification Solvent Diffusion Process

4.1.1 Introduction

This is the most widely used method for preparation of nanoparticles. In this technique, all the ingredients that are required in the final dispersed phase are solubilized in an organic solvent. The organic solvent is chosen such that it is partially soluble in water and the aqueous system is consequently saturated with the organic phase so as to keep the thermodynamic partition equilibrium of the dispersed and dispersing phases (Allemann et al. 1993). The selected polymer and the drug are dissolved in a water-immiscible organic phase and further saturated with water to ensure the thermodynamic equilibrium of both solvent systems. Successively, saturated solvent phase containing polymer-water is emulsified in an aqueous solution containing stabilizer such as polyvinyl alcohol in water which leads to solvent diffusion to the external phase and the formation of nanoparticles in solvent phase (Petros and DeSimone 2010), as shown in Fig. 12.1. Once there is a formation of emulsion, then emulsified droplets are diluted in water which leads to an interaction between emulsion droplets and dilution phase, which further leads to the precipitation of polymer due to poor solvency of polymer. In this method two possible mechanisms observed in the formation of nanoparticle are mechanism due to mechanical means and the particle formation from droplet of emulsion (Zaida Urbán et al. 2010).

4.1.2 Mechanism

Emulsion of droplet size 2–5 μm was obtained by emulsification of oil and water using mechanical shear. Successively, the slow diffusional motion of water-immiscible solvents into the aqueous phase takes place, and precipitation of polymer starts until it reaches limiting concentration for polymer; phase separation occurs from the interface. Thus, each emulsion droplet forms individual polymer nanoparticle when the solvent is extracted (Feng et al. 2010). In general, good emulsion homogenization such as in ultrasonication produces droplets with a diameter < 0.5 μm, and thus, a similar size is yielded for nanoparticles (Brannon-Peppas and Blanchette 2004).

Mechanical Mechanism

Quintanar-Guerrero et al. (2005) had proposed the mechanical approach to prepare the nanoparticle using emulsification solvent diffusion method and using principle of polymer precipitation and interfacial phenomenon. In this method, strong interfacial tension difference cannot be determined by variation of interfacial concentration due to partial water miscibility of solvent and saturation level by water to maintain equilibrium during emulsification stage. Higher concentration of stabilizing agent in this method will drastically reduce the interfacial tension which reduces the globule size up to significant level. It is also mentioned that interface between hydrophilic and lipophilic phase is exposed to high mechanical force in the process of emulsification. Shear force leads to increase in energy in molecules, and the presence of surfactant plays important role in controlling the size of nanoparticle. After complete diffusion of solvent, submicron particle will be formed if stabilizing agent is present at liquid interface (Murthy 2007).

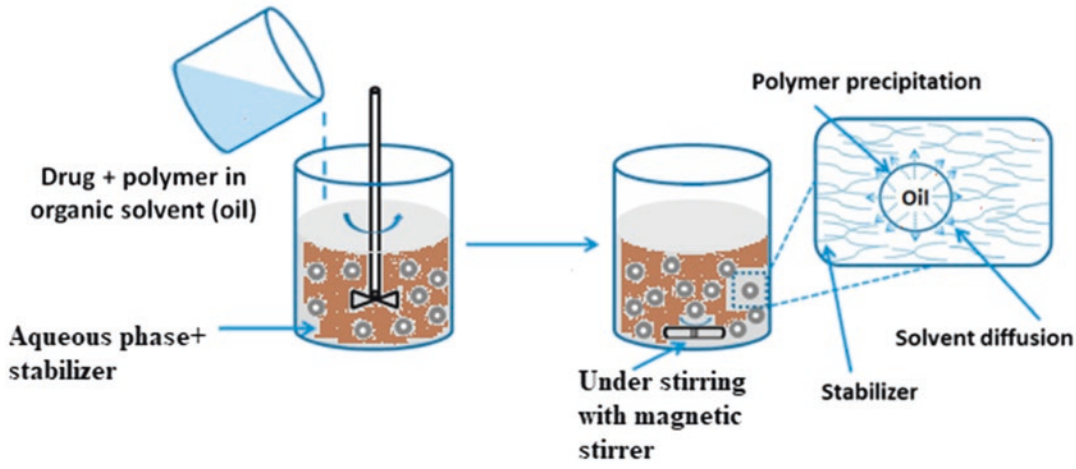

Fig. 12.1 Nanoparticle by emulsification solvent diffusion method

Formation of Particle from Emulsion Droplet

Galindo-Rodriguez et al. (2004) supported the mechanism of particle formation by this approach. It was suggested that particle size is always less than emulsion droplet. The droplet formation in organic phase was given by binary break-up mechanism in which the droplet is continuously broken down in two possible fragments until hydrodynamic condition is achieved. Also droplet formation was governed by capillary disruption in which droplet is strained to produce elongated filaments which further convert to fragment depending upon capillary number. To obtain controlled particle size, many processing parameters need to be controlled like temperature, stirring speed, stirring time, organic to aqueous phase ratio and also order of phase mixing. Aubrey et al. (2017) studied the effect of order of mixing of different phase on particle size. When organic phase was added drop wise to the aqueous phase decrease the particle size.

4.1.3 Effect of Various Factors on Controlling Size of Particles

Nature of Polymer

Nature and type of polymer highly stimulates the size and stability of nanoparticle prepared by emulsification solvent diffusion method. Zeta potential of particle is always negative if it is prepared by non-ionic stabilizing agent due to availability of carboxylic acid group in the surface of particle (Zhang et al. 2008). When the concentration of polymer is high, different behaviours are observed due to difference in molecular size and molecular arrangement. If polymer concentration is too high, then it leads to increase in particle size of particle; it may be due to the increase in viscosity which leads to Ostwald's ripening.

Effect of Stabilizing Agent

Stabilizing agent plays a key role in controlling physical stability dispersion containing submicron-level particles. Concentration and nature of stabilizing agent affect the size and stability of the particle. Stabilizing agent plays a key role as surfactant in the formation of emulsion droplet and shape formation governed by the presence of stabilizer. Stabilizing agent lowers interfacial tension between aqueous and organic phase by adsorption on the interface of solvent phase formed during emulsification step which leads to the decrease in particle size. The remaining quantity is used for preventing aggregation during dilution phase by steric, electrostatic and electro-steric effect (Xu et al. 2013).

Effect of Solvent

Solvent influences particle size and zeta potential of submicron particles. Murakami et al. (2000) suggested that particle size and yield of particles are highly influenced by affinity of polymer towards solvent. Solubility parameter and interaction parameter are used for studying the behaviour of the particle system. Lower solvent-water interaction parameter means higher solvent-water affinity for solvent diffusion. However, more polymer-solvent interaction parameter facilitates solvent diffusion. Thus, major affinity of polymer and solvent as well as solvent-water leads to larger particle size. Higher affinity of polymer solvent causes difficulty in solvent diffusion which causes insufficient solvent migration towards the external phase. Thus, particle size seems to be larger. Many physicochemical properties of solvent like surface tension, viscosity, density and water solubility affect particle size. Lower values of all these properties lower the particle size. Precipitation of particle is due to different molecular arrangement of polymeric chain obtained, depending upon solvent used. Typical organic solvents that are partially soluble in water are those of medium polarity like ethyl acetate, methyl ethyl ketone, benzyl alcohol and propylene carbonate (McNamara and Tofail 2017). Many researchers have developed nanoparticle using this emulsification solvent diffusion as shown in Table 12.1.

4.1.4 Advantages and Disadvantages

This technique gives many advantages like more encapsulation capacity compared to other method of manufacturing with no requirement for homogenization. It also gives higher batch-to-batch reproducibility with ease of scale-up, simplicity and narrow size distribution. This process allows a precise control of particle size that is difficult with other usual method of preparation of nanoparticles like nano-precipitation. Major limitation of using this technique is leakage of water-soluble drug into the external phase during emulsification which may reduce encapsulation efficiency (Kudr et al. 2017).

4.2 Emulsification Solvent Evaporation Method

4.2.1 Introduction

From the different processes for manufacturing nanoparticle, the emulsification solvent evaporation method is well recognized. It is a method with huge popularity because of its easiness, and it mainly allows effective encapsulation of various compounds which are lipophilic in nature. Emulsification solvent evaporation involves two steps. The first one consists of the dissolution of the polymer and the drug in a volatile organic solvent. In the past, dichloromethane and chloroform were frequently used, but these have now been replaced by ethyl acetate to minimize residual solvent toxicity concerns. Initially there is an aqueous phase used for emulsification of the polymer. During the second step, polymer solvent is evaporated, which leads to polymer precipitation on a central core to give nanoparticles as shown in Fig. 12.2. The nanoparticles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residue or any free drug and lyophilized for storage (Liu et al. 2008). Recently modification takes place in this method which is known as high-pressure emulsification, followed by solvent evaporation method. This method involves first preparation of emulsion followed by homogenization using high pressure, and further it is subjected to stirring to evaporate organic solvent. Various parameters like type and amount of dispersing agent, stirring rate, temperature and viscosity of both organic and aqueous phases highly influence the size of particle. Conversely this method can be applied to lipophilic drugs, and restrictions are enforced by the scale-up issue.

4.2.2 Mechanism of Formation of Nanoparticles

Mechanism of nanoparticle formation depends on type of polymer used for preparation. Coalescence of single or multiple droplets is observed in emulsion during preparation of nanoparticle. Then it is followed by stabilization using surfactant during solvent evaporation (Moinard-Chécot et al. 2008). When ethyl cellu-

Table 12.1 Drug, polymer, stabilizer and solvent used for emulsification solvent diffusion process

Sr. no.	Name of drug	Polymer	Stabilizer	Solvent	Size	References
1	Meso-tetra(hydroxyphenyl) porphyrin	PLGA (p-THPP	PVA	Dichloromethane	200 nm	Konan et al. (2003)
2	Doxorubicin	PLGA	PVA	Ethyl acetate, methanol	180 nm	Pieper et al. (2017)
3	Cyclosporine (cy-A-)	Glyceryl behenate (Compritol® ATO 888)	Lauroyl macrogolglycerides (Gelucire® 44/14)	Ethyl acetate	280 nm	Zaida Urbán (2010)
4	Lecithin and taurodeoxycholic acid sodium salt	Glyceryl monostearate	–	Benzyl alcohol	250 nm	Trotta et al. (2003)
5	Blank	PLA	PVA	Polycarbonate	212	Quintanar-Guerrero et al. (1997)
6	Omapatrilat	PLA	Poloxomer 188	Ethyl acetate	170 nm	Tamayo-Esquivel et al. (2006)
7	Docetaxel	Lecithin	PEG 2000	Chloroform	230 nm	Nijaporn et al. (2009)
8	Curcumin	PLGA	PVA	Ethylene (ETH), acetone (ACE)	180 nm	Cen et al. (2014)
9	Clobetasol propionate	Monostearin	Poloxamer 188	N hexane	250 nm	Yuan et al. (2008)
10	Rifampicin	Polycaprolactone	Pluronic F68	Ethyl acetate	100 nm	Mi-Yeon et al. (2009)
11	Blank	Poly(ε-caprolactone)	Polyvinyl alcohol	Ethyl acetate	260 nm	Asim et al. (2012)
12	Oestrogen	Poly(D,L-lactide-co-glycolide) (PLGA)	Didodecyldimethylammonium bromide (DMAB)	Propylene carbonate (PC)	100 nm	Hye-Young et al. (2001)
13	*Cymbopogon citratus*	PLGA	PVA	DCM	280 nm	Kessiane et al. (2019)
14	Insulin	HPMC	PVA	Acetone	183 nm	Fang et al. (2019)
15	Sertaconazole	Stearic acid	Labrafac	Ethanol: acetone	272 nm	Naser et al. (2019)
16	Tretinoin	Glyceryl monostearate, Compritol 888 ATO®, Dynasan 116® and Cutina CBS®	Epikuron 200®, Tween 20 and Tween 80	Benzyl alcohol	230 nm	Weissig and Elbayoumi (2019)

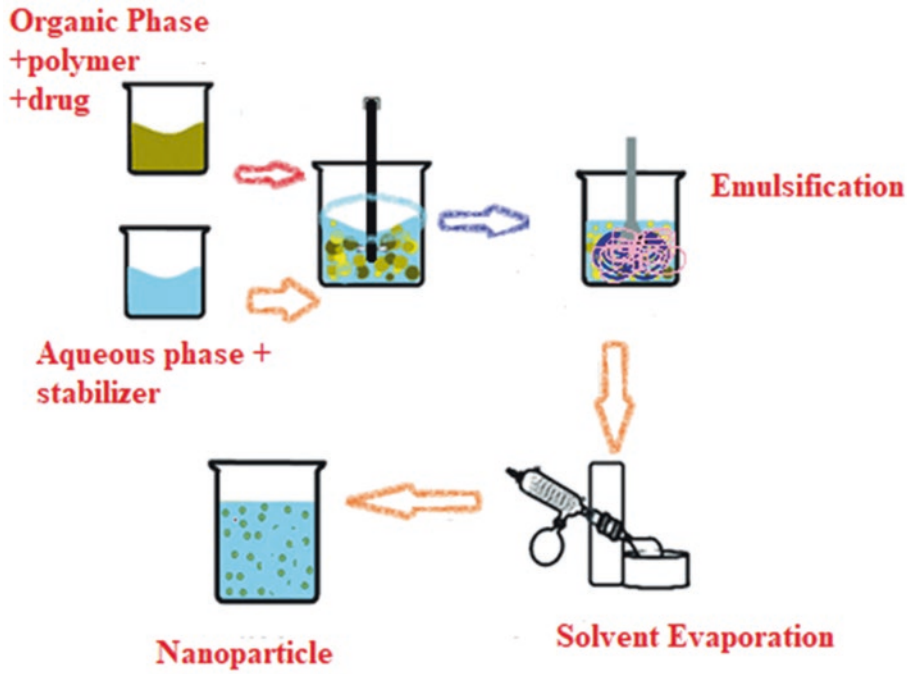

Fig. 12.2 Nanoparticle by emulsification solvent evaporation method

lose (EC) was used, emulsion droplet starts to coalescence before obtaining stable nanoparticle which is free from any traces of solvent during evaporation, and nanoparticles were generated from several droplets. In contrast, when polylactic acid (PLA) was employed, limited or no coalescence occurred; therefore, a nanoparticle was formed from a single droplet. Differences were attributed to the surface activity properties of the polymers; EC is surface active, whereas PLA has no interfacial adsorption. The major disadvantage of emulsification solvent evaporation is its poor efficiency in the incorporation of hydrophilic drugs such as peptides, proteins and genetic material (Vanderhoff et al. 1979). Many researchers have developed nanoparticle using emulsification solvent evaporation as shown in Table 12.2.

4.2.3 Factors Influencing Nanoencapsulation Process

Various factors affect final nanoparticles obtained including (a) solubility of the drug, (b) type and concentration of polymer, (c) the ratio of drug/polymer, (d) the organic solvent utilized, (e) concentration and nature of stabilizer utilized, (f) stirring speed and temperature of the emulsification process and (g) the volume and viscosities of the dispersed and continuous phases (Paliwal et al. 2014). Manipulation of these variables has been shown possible to optimize nanoparticle size and maximize efficiency of encapsulation as shown in Fig. 12.3.

Type of Polymer

Copolymers of lactic and glycolic acids (PLGA) are the most frequently used polymer to prepare nanocarrier systems due to their safety profile and Food and Drug Administration (FDA) approvals in humans. Non-biodegradability and biocompatibility property make successful use of drug carriers, like ethyl cellulose (EC) and polymethyl methacrylate. The selection of polymer used depends on the anticipated drug release pattern, which is mostly controlled by physical and chemical properties of polymer system (Khinast et al. 2013). If a single polymer system is unable to provide satisfactory drug release, then copolymer is manufactured from two individually different polymers. The characteristics of the

Table 12.2 Drug, polymer, stabilizer and solvent used for emulsification solvent evaporation process

Sr. no.	Drug	Polymer	Stabilizer	Solvent	Particle size	References
1	Paclitaxel	PLGA and vitamin E TPGS	PVA, Poloxomer 188	Dichloromethane	230 nm	Navneet et al. (2016)
2	Ketoprofen	Eudragit E100 Eudragit RS 100	PVA	Acetone	120 nm	Le Thi (2012)
3	Aceclofenac	Ethyl cellulose	PVA	Dichloromethane	10 um	Gupta et al. (2013)
4	Rifampicin	PLGA	PVA	Dichloromethane	360 nm	Tripathi et al. (2010)
5	Haemagglutinin (HA)	PLGA	PVA	Dichloromethane	216 nm	Lemoine and Preat (1998)
6	Zidovudine	PLA	PVA	Methylene chloride	320 nm	Mainardes et al. (2010)
7	Progesterone	Poly(hydroxybutyrate-co-hydroxyvalerate), poly(ε-caprolactone) poly(L-lactic acid)	PEG	Chloroform	140 nm	Fernanda et al. (2015)
8	Ketoprofen	Eudragit E100	Sodium dodecyl sulphate	Chloroform	150 nm	Le Thi (2009)
9	Levofloxacin	Poly(lactic-co-glycolic acid) (PLGA) and chitosan (CS)	PVA	Dichloromethane	430 nm	Manuel et al. (2019)
10	Praziquantel	Poly(D,L-lactide-co-glycolide) (PLGA)	PVA	Methylene chloride		Rubiana et al. (2006)
11	Dexamethasone	PLGA	PVA	Acetone		Seda et al. (2019)

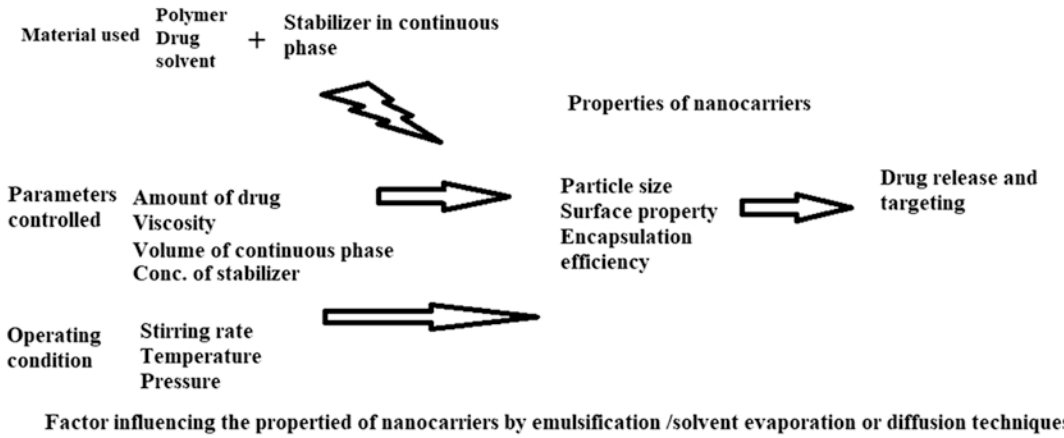

Fig. 12.3 Factors affecting nanoparticle properties using emulsification solvent evaporation

copolymer are enhanced because it consists of two segments on the chain like PLGA.

The Organic Solvent

Emulsification solvent evaporation has some specific selection criteria for solvent like ability to dissolve the chosen polymer and having poor solubility in the external phase; solvent with high volatility, low toxicity and a low boiling point is expected. Methylene chloride is the most effective solvent for the preparation of nanoparticle because of its rapid evaporation which may be due to low boiling point and also high level of immiscibility with water. More solvent evapora-

tion rate of methylene chloride may be due to high vapour pressure compared to other solvents. Chloroform was frequently used earlier but it is progressively substituted by methylene chloride due to its toxicity and relatively low vapour pressure. The commonly used solvents in this method are dichloromethane (DCM) and ethyl acetate. Other more toxic solvents used are chloroform and acetonitrile. When single organic solvent is not able to solubilize the drug, a mixture of solvent is required; the most commonly used solvent mixture is DCM-ethanol (Sovan et al. 2011).

Concentration and Type of Stabilizer

The surfactant is normally engaged in the distribution of aqueous phase in to its immiscible phase and for the maintenance of equilibrium condition in emulsion. It diminishes the surface tension of external phase, prevents the amalgamation and accumulation of drops and stabilizes the emulsion. A selection of proper surfactant is able to give nanoparticle of a regular size and a controlled particle size distribution, with a more expectable and stable drug release. Depending upon nature of the hydrophilic part of surfactant molecule, they are classified as non-ionic, anionic, cationic and amphoteric. For the mostly prepared emulsion using methylene chloride/water, typical non-ionic stabilizers like partially hydrolysed PVA, methylcellulose, tweens and spans as well as anionic surfactant like sodium dodecyl sulphate were used (Rao and Geckeler 2011). Commonly used stabilizers include polyvinyl alcohol (PVA), poloxamer 127, poloxamer 188 and polysorbate 80 among others.

Stirring Speed and Temperature of the Emulsification Process

Speed of stirring will control the particle size and its uniformity. The solvent evaporation rate can be enhanced either by increasing the temperature of the continuous phase or by reducing the use of vacuum to reduce pressure in the reactor.

The Volume and Viscosities of the Dispersed and Continuous Phases

Viscosity of dispersed phase was proportionally related to the polymer concentration and the molecular weight. Increasing viscosity also improves entrapment efficiency and size also. Polymers used in this method are PLGA, polyglycolic acid (PGA), PLA, ethyl cellulose (EC), cellulose acetate phthalate (CAP), polycaprolactone (PCL), poly(hydroxybutyrate) (PHB) and poly(β-hydroxybutyrate) (PBHB) (Mody et al. 2010).

5 Advanced Emulsification Techniques

5.1 Membrane Emulsification

In high-pressure homogenization and ultrasonication, there is a stability issue of potential candidate due to high-energy input which leads to the progress of membrane emulsification solvent evaporation method. This method combined emulsification by low-energy conventional process and premix membrane emulsification has been proposed. The coarse emulsion obtained by low-speed stator homogenization is extruded through membrane under excess pressure to form uniform-sized nanoparticles. In premix membrane emulsification process for nanoparticle preparation, the size of the coarse emulsions was reduced to nanoscale due to high transmembrane pressure which leads to droplet disruption. The most commonly used membranes for oil-in-water emulsions are hydrophilic Shirasu porous glass (SPG) membranes and for water-in-oil emulsions polytetrafluoroethylene (PTFE) membranes. The solvent present in the nanoemulsion is removed either by prolonged stirring or evaporating under vacuum conditions. The solvent commonly used is ethyl acetate due to its relatively high boiling point. SPG membrane pore size is critical to the manufacturing of uniformly sized nanoparticles. Droplet size can be controlled by the membrane type, the crossflow velocity and the transmembrane pressure; with increased transmembrane pressure, small-sized particles with narrow-sized distribution were obtained. Advantages of this modification cover narrow-sized distribution of nanoparticle and high productivity, simplicity and suitability for synthetic and natural polymers (Liu et al. 2010). Biodegradable materials such as

poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), sodium alginate, chitosan, polylactide (PLA), Eudragit, etc. are employed.

Qiang Weim et al. (2008) had developed nanoparticles by a simplistic method combining premix membrane emulsification followed by solvent removal for the first time. Initially there is a preparation of coarse emulsions, additional premix membrane emulsification with very high pressure was employed to achieve uniform-sized nanodroplets, and nanoparticles were formed by further solidification. Polylactide was designated as a model polymer. Type of organic solvent, the volume ratio of oil phase and external water phase, pore size of the microporous membrane and transmembrane pressure played key roles for the size of nanoparticle. The novel method also has the advantages of high productivity, simplicity and easy scale-up.

5.2 High-Pressure Emulsification

The nanometric size of the emulsion droplet is controlled by applying high-shear forces usually by high-speed stirring or ultrasonication. Another way to obtain very-small-sized oily globules is by means of a high-pressure homogenizer. In general, the high-pressure emulsification and solvent evaporation method consist of forming a coarse emulsion with the polymer and the drug in an organic solvent and an aqueous solution with a stabilizer agent; this emulsion is transferred into a high-pressure homogenizer, and the emulsification is performed at high pressure by recycling the emulsion by several cycles (Jaiswal et al. 2004). High-pressure emulsification has been employed to prepare pharmaceutical nanoemulsions.

Lamprecht et al. (1999) investigated nanoparticles as effective drug carriers for biological proteins. The bovine serum albumin is a hydrophilic protein which is incorporated within NP. The double emulsification has been chosen due to high solubility of the protein in water using a Microfluidizer as homogenization device with PLGA and PCL polymer and has been used for the preparation of the nanoparticles. The bovine serum albumin encapsulation was high up to 80%, and drug release pattern was categorized by a significant initial rapid release for both PLGA and PCL nanoparticle. An increased release rate was attained at the last dissolution study for PLGA nanoparticle up to 92% compared with PCL nanoparticle up to 72%.

5.3 Microchannel Emulsification

Microchannel technology was proposed to prepare tiny microchannels embedded in silicon plate. Emulsified droplets are formed by pushing the dispersed phase through the microchannels. Microchannel emulsification decreases interfacial tension, which is the driving force for formation of droplets (Kawakatsu et al. 1997).

Sugiura et al. (2004) developed aqueous multiple emulsion by double emulsification using microchannel emulsification in second step. They used a high-speed homogenizer for the initial phase of emulsification step due to low output rate of microchannel emulsification.

6 Conclusion

The major aim of this chapter is to highlight the different manufacturing techniques accessible for manufacturing of nanoparticles. It was perceived that among the various possible available methods, nanoparticle requires a suitable selection of technique. Depending on the physical and chemical properties of a drug, it is promising to select the most suitable method for manufacturing and a suitable polymer to produce nanoparticles with preferred particle size with good drug loading efficiency. Methods used to prepare nanoparticle like emulsification solvent diffusion and solvent evaporation are simple, and they rely on the use of pharmaceutically acceptable solvents, biocompatible polymers and surfactants. The versatility of both these methods is demonstrated by the use of modified polymers to enable the production of modified nanoparticle with control particle size and targetability. Reports on the scale-up and production of large batches of nanoparticles in a reproducible way using emulsification solvent diffusion and evaporation are expected to increase.

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