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1 **Particles from preformed polymer as carriers for drug delivery**

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13 14 **Abstract:**

15 Biodegradable and biocompatible polymers are widely used for the encapsulation of drug
16 molecules. Various particulate carriers with different sizes and characteristics have been
17 prepared by miscellaneous techniques. In this review, we reported the commonly used
18 preformed polymer based techniques for the preparation of micro and nano-structured
19 materials intended for drug encapsulation. A description of polymer solvent interaction was
20 provided. The most widely used polymers were reported and described and their related
21 research studies were mentioned. Moreover, principles of each technique and its crucial
22 operating conditions were described and discussed. Recent applications of all the reported
23 techniques in drug delivery were also reviewed.

24 **Introduction:**

25 Particulate carriers have gained tremendous interest during the last decades which permitted
26 to deliver many hydrophilic and hydrophobic molecules. Obtained particles present small size
27 which facilitates their absorption. These drug delivery systems allow the protection of active
28 pharmaceutical ingredients from degradation, enhance biopharmaceutical properties and could
29 provide passive or active targeting or sustained delivery. Biomedical applications of the
30 developed carriers are continuously growing ([Ahmad 2013](#))([Soares 2013](#))([Miladi et al. 2013](#)).
31 Although, they present different physicochemical properties, the used polymers are mainly
32 biocompatible and biodegradable. A multitude of techniques are used to obtain these particles.
33 These methods differ by their principles and the nature of drug molecules that could be
34 encapsulated. Some successfully marketed products led to an enlargement of the applications
35 and the interest given by researchers to these drug delivery systems. Choice of the technique
36 and operating conditions is crucial to obtain formulations bearing good properties for *in vitro*

37 and *in vivo* applications. In this review, we will focus on polymeric nanoparticles and give a
38 scope about the most used polymers. We will also describe the common preformed polymer
39 based techniques used for the encapsulation of drug molecules. We will also review the major
40 applications of the developed particles during the last years and their main properties.

41 1. Polymer solvent interactions:

42 A lot of techniques that rely on preformed polymers have been used for the preparation of
43 particulate carriers. Although these methods are quite different, they generally share a unique
44 principle which is polymer precipitation. Precipitation of the polymer occurs either when a
45 non solvent is added or after subsequent decrease of its solubility in a solvent. Many
46 parameters could influence polymer solubility such as, solvent nature, pH, salinity and
47 temperature of the dispersion medium. Solubility of polyelectrolytes in water, for example, is
48 highly pH and salinity dependent (Gennes 1979), while that of poly(alkyl acrylamide) and
49 poly(alkyl methacrylamide), is mainly temperature dependent (Elaissari 2002). In fact,
50 nanoprecipitation and emulsion based techniques are based on the addition of a non solvent to
51 the polymer which causes its precipitation. However, ionic gelation technique, for instance, in
52 which generally a polyelectrolyte is used as polymer, is based on the addition of a salt or an
53 oppositely charged polymer. This results in a change in the salinity of the medium and the
54 appearance of electrostatic interactions and thus, leads to polymer precipitation. The
55 thermodynamic behavior of the polymer in a given solution is highly dependent on the Flory
56 χ -parameter. This parameter is defined as the free energy change per solvent molecule (in $k_B T$
57 units) when a solvent-solvent contact is shifted to a solvent-polymer contact. It is expressed
58 by the following mathematical equations:

59 Tapez une équation ici.

$$60 \quad \chi = \frac{\Delta G}{k_B T} = \frac{\Delta H - T\Delta S}{k_B T} = \frac{1}{2} - A\left(1 - \frac{\theta}{T}\right) \quad \text{Equation (1)}$$

61 Where k_B and T are Boltzmann constant and temperature, respectively; A and θ parameters
62 are defined as follow:

$$63 \quad A = \frac{2\Delta S + k_B}{2k_B} \quad \text{Equation (2)}$$

$$64 \quad \theta = \frac{2\Delta H}{2\Delta S + k_B} \quad \text{Equation (3)}$$

65

66 It can be seen that the A parameter is directly related to entropy changes, whereas θ
67 temperature is a function of both entropic and enthalpic variations. When θ temperature = T ,
68 the corresponding Flory χ -parameter = 1/2, at which the second Virial coefficient is equal
69 zero (Elias 2003). The latter can be easily determined from light scattering measurements of a
70 diluted polymer solution. At θ temperature conditions, the binary interactions among
71 constituents will be negligible and only the excluded volume effects will be predominant.

72 Consequently, the solvent will be a good solvent for the polymer when $\chi < 1/2$ and a poor one
73 when $\chi > 1/2$ (Minost et al. 2012).

74 **2. Commonly used polymers for encapsulation:**

75 A lot of polymers have been used for drug encapsulation but only biodegradable and
76 biocompatible polymers are suitable for biomedical applications. The biodegradability of a
77 polymer is acquired by the presence of a labile function such as ester, orthoester, anhydride,
78 carbonate, amide, urea or urethane in their backbone. These polymers could be of natural
79 (polysaccharides and protein based polymers) or synthetic (polyesters) nature (Pillai &
80 Panchagnula 2001). The most commonly used polymers for drug encapsulation are polyesters
81 (lactide and glycolide copolymers, poly- ϵ -caprolactone), acrylic polymers
82 (polymethacrylates) and polyamides (gelatin and albumin). The selection of the right polymer
83 is a crucial step to obtain particles that are suitable for a well-defined application. In fact,
84 polymers' structures are highly different and their surface and bulk properties are highly
85 relevant for the obtaining of the desirable biological application. Copolymers could be also
86 used to monitor the hydrophobicity of the materials. Some polymers are poly(ethyleneglycol)
87 (PEG) copolymerized in order to decrease nanoparticle recognition by the reticular
88 endothelial system. Table 1 contains examples of the most used biocompatible and
89 biodegradable polymers in encapsulation. Some polymers, especially those having
90 mucoadhesive properties, could also be used for coating the nanocarriers (Mazzaferro et al.
91 2012)(Zandanel & Vauthier 2012).

92 **2.1.Natural polymers:**

93 **2.1.1. Chitosan:**

94 Chitosan is obtained by deacetylation of chitin, which is the structural element in the
95 exoskeleton of crustaceans (crabs, shrimp, etc.) and cell walls of fungi. It is a cationic and
96 biodegradable polysaccharide consisting of repeating D-glucosamine and N-acetyl-D-
97 glucosamine units, linked via (1-4) glycosidic bonds. Chitosan is non toxic and can be
98 digested in the physiological environment, either by lysozymes or by chitinases, which are
99 present in the human intestine and in the blood. These properties led to increased interest for
100 this polymer in pharmaceutical research and in industry as a carrier for drug delivery (Mao et
101 al. 2010). In addition, chitosan has mucoadhesive properties owing to its positive charge that
102 allows interaction with the negatively-charged mucosal surface. Consequently, the use of
103 chitosan as a matrix (Patil & Sawant 2011) or as a coating material (Mazzarino et al. 2012) in
104 drug encapsulation had become a promising strategy to prolong the residence time, to increase
105 the absorption of active molecules through the mucosa (Mao et al. 2010)(Alpar et al. 2005)
106 and also for targeted delivery (Park et al. 2010).

107

108 **2.1.2. Dextran and its derivatives:**

109 Dextran polymers are produced by bacteria from sucrose. Chemical synthesis is also possible.
110 These glucose polymers consist predominantly of linear α -1,6-glucosidic linkage with some
111 degree of branching via 1,3-linkage. Dextran-based microspheres have got much attention
112 because of their low toxicity, good biocompatibility and biodegradability, which are of

113 interest for application in biomedical and pharmaceutical fields (Mehvar 2000). Many dextran
114 polymers such as Sephadex® (cross-linked dextran microspheres) as well as Spherex®
115 (cross-linked starch microspheres) were used as carriers for drug delivery. Other derivatives
116 of dextran and starch including diethyl aminoethyl dextran and polyacryl starch have also
117 been used for mucosal drug delivery. Illum *et al.* proposed some mechanisms to explain
118 absorption enhancement effects of cross-linked starch and dextran microspheres intended to
119 nasal delivery which are: (1) Deposition of the microspheres in the less or non ciliated
120 anterior part of the nasal cavity and slower nasal clearance; (2) Retention of the formulation in
121 the nasal cavity for an extended time period because of the bioadhesive properties of the
122 microspheres and (3) The local high drug concentration provided by the gelled system in
123 close contact with the epithelial absorptive surface (Illum *et al.* 2001).

124

125 **2.1.3. Cyclodextrins:**

126 Cyclodextrins (CDs) are cyclic oligosaccharides that contain at least six D-(+) glucopyranose
127 units which are attached by α -(1,4) glucosidic bonds. They have been widely used for the
128 formulation of drugs with bioavailability concerns resulting from poor solubility, poor
129 stability and severe side effects. There are 3 natural CDs which are α -, β -, and γ -CDs (with 6,
130 7, or 8 glucose units respectively) (Challa *et al.* 2005). In addition, amphiphilic cyclodextrins
131 are synthetic derivatives of natural cyclodextrins. Such derivatives are able to self-organize in
132 water to form micelles and nano-aggregates, which is interesting for pharmaceutical
133 applications, mainly, encapsulation (Gèze *et al.* 2002). In fact, amphiphilic cyclodextrins have
134 recently been used to prepare nanoparticles and nanocapsules without surfactants and have
135 shown high drug-loading capacity with favorable release properties (Lemos-Senna *et al.*
136 1998)(Çirpanlı *et al.* 2009)(Duchêne 1999). They have also been used for targeting and for
137 increasing drug loading (Duchêne *et al.* 1999).

138

139 **2.1.4. Gelatin:**

140 Gelatin is a natural polymer that is derived from collagen. It is commonly used for
141 pharmaceutical and medical applications because of its biodegradability and biocompatibility
142 in physiological environments. Gelatin is attractive for use in controlled release due to its
143 nontoxic, bioactive properties and inexpensive price. It is also a polyampholyte having both
144 cationic and anionic groups along with hydrophilic groups. Mechanical properties, swelling
145 behavior and thermal properties of gelatin depend significantly on its crosslinking degree.
146 (Young *et al.* 2005).

147

148 **2.2. Biodegradable polyesters:**

149 Polyester-based polymers are among of the most widely investigated materials for drug
150 delivery. Poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers poly(lactic
151 acid-co-glycolic acid) (PLGA) along with poly- ϵ -caprolactone are some of the well-defined
152 biomaterials with regard to design and performance for drug-delivery applications.

153

154 **2.2.1. PLGA:**

155

156 PLGA, a copolymer of lactic acid and glycolic acid, has generated tremendous interest due to
157 its excellent biocompatibility, biodegradability, and mechanical strength. PLGA is approved
158 by the US FDA and European Medicine Agency (EMA) in various drug delivery systems in
159 humans. In order to improve the formulation of controlled drug delivery systems, an
160 understanding of the physical, chemical, and biological properties of polymers is helpful. In
161 fact, the polymer is commercially available with different molecular weights and copolymer
162 compositions. The degradation time can vary from several months to several years, depending
163 on the molecular weight and copolymer ratio (Danhier et al. 2012). For example, lactic acid is
164 more hydrophobic than glycolic acid and, therefore, lactide-rich PLGA copolymers are less
165 hydrophilic, absorb less water, and subsequently, degrade more slowly (Dinarvand et al.
166 2011). PLGA particles are widely used to encapsulate active molecules with a broad spectrum
167 of pharmaceutical applications (Danhier et al. 2012)(Menei et al. 2005)(Singh et al. 2004).

168

169 **2.2.2. PLA:**

170

171 PLA is a biocompatible and biodegradable synthetic polyester which undergoes scission in
172 the body to monomeric units of lactic acid. The latter is a natural intermediate in carbohydrate
173 metabolism. PLA possess good mechanical properties and it is largely used for the
174 preparation of particles (Gupta & Kumar 2007).

175

176 **2.2.3. PCL:**

177 It was in 1930s that the ring-opening polymerization of PCL was studied. The biodegradable
178 property of this synthetic polymer was first identified in 1973. PCL is suitable for controlled
179 drug delivery due to its high permeability to many drugs and non-toxicity (Sinha et al. 2004).
180 Molecular weight dependent surface hydrophobicity and crystallinity of PCL are the causes
181 for its slower biodegradation in two distinct phases such as random non-enzymatic cleavage
182 and enzymatic fragmentation. The lipophilic drugs are generally distributed uniformly in the
183 matrix while the hydrophilic drugs tend to move towards the interface and remain on the
184 surface of PCL formulation in adsorbed state. Diffusion was described as the only possible
185 mechanism by which the lipophilic drugs release from PCL particles as they were shown to be
186 intact for a much longer duration *in vivo*. However, two phenomenons could be implicated in
187 hydrophilic drugs' release. Highly lipophilic drugs that resist complete diffusion are released
188 upon surface erosion by enzymatic action while hydrophilic drugs that accumulate at the
189 interface during the formulation processes are released by desorption at the initial period of
190 release study or dosage intake. This results in a biphasic drug release pattern for PCL particles
191 with much higher burst release for hydrophilic drugs than lipophilic ones (Dash &
192 Konkimalla 2012).

193

194 **2.3. Pegylated polymers:**

195 A lot of the above cited polymers could be conjugated to PEG chains, which allows the
196 enhancement of their hydrophilicity and permits the obtaining of a stealth surface that could
197 protect the prepared carriers from degradation by the cells belonging to the reticuloendothelial
198 system. Conjugation to PEG confers also bioadhesive properties for the carriers (Yoncheva et
199 al. 2005).

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201
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203
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205

Table 1. Commonly used polymers

Materials	References
Polymers	
<i>Natural polymers</i>	
Chitosan	(Elmizadeh et al. 2013)(Fàbregas et al. 2013) (Khalil et al. 2012) (Konecsni et al. 2012)(Du et al. 2009)(Bernkop-Schnürch et al. 2006) (Gan et al. 2005) (Asada et al. 2004)
Dextran	(Liang et al. 2013) (Dai et al. 2012)(Sajadi Tabassi et al. 2008) (Koten et al. 2003)
Dextran derivatives	(Kanthamneni et al. 2012)(Kauffman et al. 2012) (Aumelas et al. 2007) (Miyazaki et al. 2006)
Cyclodextrins	(Çirpanli et al. 2009) (Memişoğlu et al. 2003) (Pariot et al. 2002)(Lemos-Senna et al. 1998)
Gelatin	(Nahar et al. 2008) (Balthasar et al. 2005) (Vandervoort & Ludwig 2004) (Bruschi et al. 2003)
<i>Synthetic polymers</i>	
<i>Biodegradable polyesters</i>	
PLGA	(Gyulai et al. 2013) (Beck-Broichsitter et al. 2012) (Morales-Cruz et al. 2012) (Beck-Broichsitter et al. 2011)(Nehilla et al. 2008) (Song et al. 2008)(Budhian et al. 2007) (Bozkir & Saka 2005)(Fonseca et al. 2002)(Yang et al. 1999) (Govender et al. 1999)
PLA	(Bazylińska et al. 2013)(Fredriksen & Grip 2012) (Kadam et al. 2012) (Kumari et al. 2011) (Ataman-Önal et al. 2006) (Lamalle-Bernard et al. 2006) (Hyvönen et al. 2005) (Katare et al. 2005) (Chorny et al. 2002) (Leo et al. 2000)
PCL	(Behera & Swain 2012)(Guerreiro et al. 2012) (Hernán Pérez de la Ossa et al. 2012) (Khayata et al. 2012) (Arias et al. 2010) (Wang et al. 2008)(Limayem Blouza et al. 2006) (Tewa-Tagne et al. 2006) (Yang et al. 2006) (Le Ray et al. 2003)(Chawla & Amiji 2002) (Raval et al.) (Hombreiro Pérez et al. 2000) (Benoit et al. 1999) (Masson et al. 1997)
poly(lactide-co-glycolide-co-caprolactone)	(Zhang et al. 2006)
<i>Acrylic polymers</i>	
Eudragit	(Hao et al. 2013)(Das et al. 2010) (Eidi et al. 2010)(Trapani et al. 2007)(Galindo-Rodríguez et al. 2005) (Haznedar & Dortunç 2004) (Pignatello et al. 2002)
<i>Others</i>	
Polyvinylbenzoate	(Labruère et al. 2010)
Pegylated polymers	
Chitosan-PEG	(Seo et al. 2009)
MPEG-PCL	(Falamarzian & Lavasanifar 2010)(Xin et al. 2010)

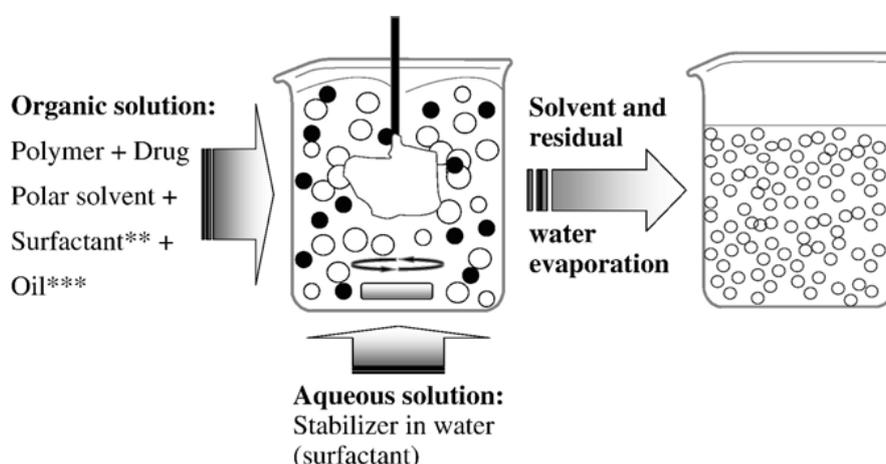
PCL-PEG-PCL	(Suksiriworapong et al. 2012)(Huang et al. 2010)(Gou et al. 2009)
poly(caprolactone)- poly(ethylene oxide)- polylactide	(Hu et al. 2003)
PLA-PEG	(Sacchetin et al. 2013) (Essa et al. 2010) (Ishihara et al. 2010) (Vila et al. 2005) (Vila et al. 2004) (Govender et al. 2000) (Huang et al. 1997)
PLA-PEG-PLA	(Chen et al. 2011)(Ruan & Feng 2003)
MPEG-PLA	(Zheng et al. 2010)(Dong & Feng 2007)(Dong & Feng 2004)

206

207 3. Used methods for the encapsulation of active molecules:

208 3.1.Nanoprecipitation:

209



210

211 *Figure 1. the nanoprecipitation technique* (Pinto Reis et al. 2006)

212

213 The nanoprecipitation technique was first developed by Fessi *et al.* in 1986 (Deviessaguet et al.
 214 1991). The technique allows the obtaining of either nanospheres or nanocapsules. The organic
 215 phase could be added to the aqueous phase under magnetic stirring. This one-step process
 216 allows the instantaneous and reproducible formation of monodisperse nanoparticles.
 217 Nanoprecipitation is simple, is by far the fastest, most reproducible, and industrially feasible
 218 preparation procedure of nanospheres (Vauthier & Bouchemal 2009). Practically, two
 219 miscible phases are required: an organic solvent in which the polymer is dissolved and an
 220 aqueous phase (non-solvent of the polymer). The most common used organic solvents are
 221 ethanol and acetone. Such solvents are miscible in water and easy to remove by evaporation.
 222 Some oils could be added to these solvents to allow the dissolving of the active (Rosset et al.
 223 2012). As Figure 1 shows, the method is based on the addition of one phase to the other under
 224 moderate magnetic stirring which causes the interfacial deposition of a polymer after
 225 displacement of the organic solvent from the organic solution. This leads to the formation of a
 226 suspension of nanoparticles. The organic phase could be a mixture of solvents such as,

227 mixture of acetone with water or ethanol etc. Similarly, the aqueous phase could consist of a
228 mixture of non-solvents and could contain surfactants. Commonly used polymers are
229 biodegradable polyesters, especially poly- ϵ -caprolactone (PCL), poly(lactide) (PLA) and
230 poly(lactide-co-glycolide) (PLGA) (Rao & Geckeler 2011). Particle formation process
231 includes three basic steps which are, particle nucleation, molecular growth and aggregation.
232 The rate of every step has a crucial impact on the particle size distribution. Supersaturation is
233 the driving force that manages all of these steps, namely, particles nucleation rate.
234 Supersaturation, itself, is influenced by fluid dynamics and mixing. In fact, low stirring rate
235 results in low nucleation rates while higher mixing rates give high nucleation rates (Lince et
236 al. 2008).

237 Operational parameters that should be controlled include the organic phase to non organic
238 phase ratio, the concentration of the polymer and the stabilizer and the amount of the drug.
239 Every one of these parameters may exert an impact on the characteristics of the obtained
240 nanoparticles (size, uniformity and charge). In fact, an increase of the polymer amount
241 generally increases particles' size (Chorny et al. 2002)(Simşek et al. 2013)(Dong & Feng
242 2004)(Asadi et al. 2011). The same effect was obtained after increasing the polymer
243 molecular weight (Limayem Blouza et al. 2006)(Holgado et al. 2012). These findings were
244 explained by an increase of the viscosity of the organic phase which rendered solvent
245 diffusion more difficult and thus, led to larger nanoparticles' size. The effect of increasing
246 organic phase volume seems conflicting: some studies showed that it causes a decrease of the
247 particles size (Dong & Feng 2004) while others showed the opposite phenomenon (Asadi et
248 al. 2011). Increasing the water phase amount lead to a decrease of the particles size as a result
249 to the increased diffusion of the water-miscible solvent in the aqueous phase and thus, the
250 more rapid precipitation of the polymer and formation of nanoparticles (Budhian et al. 2007).
251 An increase of the surfactant amount generally causes a decrease of the particles size and
252 reduces size distribution (Contado et al. 2013) (Siqueira-Moura et al. 2013). Some studies did
253 not, however, found significant change following surfactant amount increase (Dong & Feng
254 2004). The nature of the surfactant may also influence the particles' size (Limayem Blouza et
255 al. 2006). Increasing mixing rate decreases the particles size as it causes faster diffusion rate
256 (Asadi et al. 2011). Theoretical drug loading may also influence particles size and drug
257 loading (Govender et al. 1999). Nanoprecipitation is generally designed for the encapsulation
258 of hydrophobic drug molecules (Seju et al. 2011)(Katara & Majumdar 2013)(Seremeta et al.
259 2013). Such actives may be dissolved within the organic phase. Bilalti *et al.* described a
260 nanoprecipitation technique intended to the encapsulation of hydrophilic molecules but the
261 size of the obtained particles was not sufficiently uniform (Bilati et al. 2005). To further
262 improve the reproducibility of the nanoprecipitation technique and make it more convenient
263 for industrial applications, membrane contactor and microfluidic technology were
264 successfully used (Khayata et al. 2012)(Xie & Smith 2010). These techniques allow better
265 size control within different batches of particles. Table 2 contains some examples of the
266 applications of the nanoprecipitation technique for drug delivery during the last years. It can
267 be concluded that polyesters are among the most used polymers for the preparation of the
268 nanoparticles by this technique.

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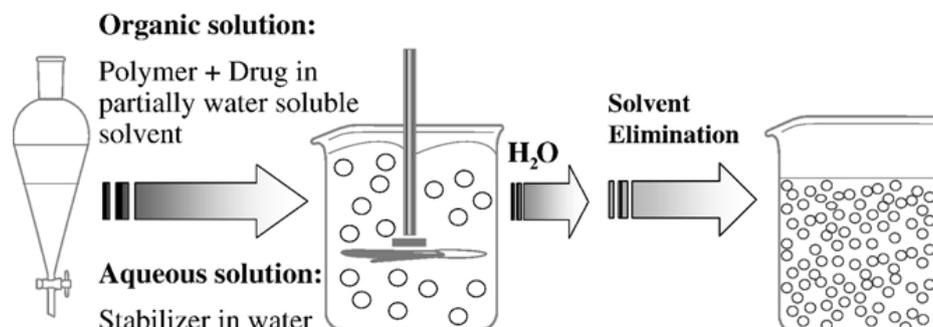
Table 2. Some applications of the nanoprecipitation technique

Encapsulated molecule	Polymer	Size (nm)	Zeta potential (mV)	Reference
Doxorubicin	Gelatin-co-PLA-DPPE	131.5-161.1	-	(Han et al. 2013)
Aceclofenac	Eudragit RL 100	75.5-184.4	22.5 - 32.6	(Katara & Majumdar 2013)
Doxorubicin	dextran-b-polycaprolactone)	95-123.3	-	(Li et al. 2013)
Chloroaluminum phthalocyanine	PLGA	220.3-326.3	-17.7-(-40.9)	(Siqueira-Moura et al. 2013)
Efavirenz	PCL and Eudragit® RS 100	89.5 - 173.9	-17.9-53.8	(Seremeta et al. 2013)
Paclitaxel	PLGA	50 - 150	-15 - (-20)	(Wang et al. 2013)
Retinoic acid	PLA	153.6-229.8	-27.4-(-20.9)	(Almouazen et al. 2012)
Brimonidine Tartrate	Eudragit® RL 100	123.5 - 140.2	13.1- 20.8	(Khan et al. 2012)
Vitamin E	PCL	123-320	-24.5-(-1.46)	(Khayata et al. 2012)
Paclitaxel	hydrophobized pullulan	127.6-253		(Lee et al. 2012)
Curcumin	PCL, chitosan	104-125	(-0.099)-79.8	(Mazzarino et al. 2012)
Diclofenac	PCL	152	-50	(Mora-Huertas et al. 2012)
Amphotericin B	PLGA	86-153	-31.4-(-9.1)	(Van de Ven et al. 2012)
Epirubicin	poly(butyl cyanoacrylate)	217-235	-4.5-(-0.1)	(Yordanov 2012)
Camptothecin	beta-cyclodextrin PLGA PCL	281 187 274	-13 -0.06 -19	(Cirpanlı et al. 2011)
Naringenin	Eudragit® E	90	-	(Krishnakumar et al. 2011)

Olanzapine	PLGA	91.2	-23.7	(Seju et al. 2011)
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274

275 **3.2.Emulsion diffusion (ESD):**



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277

278

279

Figure 2. Emulsion diffusion technique (Pinto Reis et al. 2006)

280

ESD was first developed by Quintanar-Guerrero and Fessi (Quintanar-Guerrero et al. 1996) to prepare PLA based nanospheres. Three liquid phases are needed in this technique: an organic phase, an aqueous phase and a dilution phase. The organic phase generally contains the polymer and the hydrophobic drug. The aqueous phase is a solution of a stabilizing agent while the dilution phase usually consists of a large volume of water. Mutual saturation of the aqueous and organic phase allows further obtaining of a thermodynamically equilibrated emulsion upon high speed homogenization. Subsequent addition of an excess of water enables the diffusion of the organic solvent from the dispersed phase resulting in precipitation of the polymer and the formation of the particles (Figure 2). Commonly used polymers in this method include PCL, PLA and Eudragit® (Mora-Huertas et al. 2010). Table 3 shows that the technique is mainly used for the encapsulation of hydrophobic molecules. However, hydrophilic molecules may also be encapsulated by a modified solvent diffusion method using an aqueous inner phase (Ma et al. 2001). Operating conditions affecting the size of the obtained particles include external/internal phase ratio, emulsification stirring rate, volume and temperature of water for dilution, polymer amount and concentration of the stabilizer (Quintanar-Guerrero et al. 1996)(Mora-Huertas et al. 2010). Influence of high shear homogenization and sonication on the particles size was assessed and it was found that sonication was more efficient for particle size reduction. The nature of the surfactant influenced also the particles size. In fact, when Pluronic F68 (PF68), didodecyldimethylammonium bromide (DMAB) and polyvinylalcohol (PVA) were compared, DMAB gave the smallest particles but with the lowest encapsulation efficiency (Jain et al. 2011). Particles size was also described to increase with an increase of initial drug amount (Youm et al. 2012), polymer amount (Youm et al. 2012)(Esmaeili et al. 2011) and the oil phase volume (Esmaeili et al. 2011)(Poletto et al. 2008). An increase of the surfactant amount resulted in a decrease of the size but it seems that above some level further significant size reduction is no longer possible (Jain et al. 2011)(Surassmo et al. 2010). An increase of the homogenization rate led to a decrease of the particles' size (Jain et al. 2011)(Kwon et al. 2001)(Galindo-Rodríguez et al. 2005). Likely, the same effect was obtained following an

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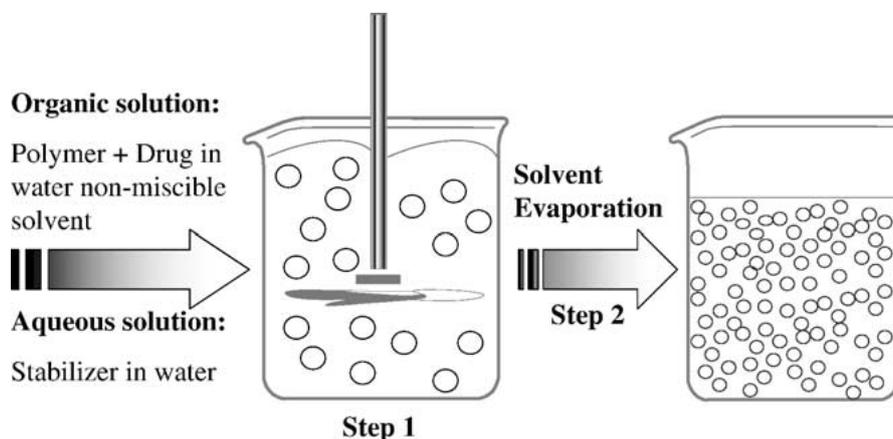
308 increase of the temperature and the volume of the added water also decreases particles' size
 309 (Kwon et al. 2001)(Song et al. 2006). The nature of the organic solvent also influenced
 310 particle size (Song et al. 2006). Table 3 shows some of the recent applications of the ESD
 311 technique.

312
 313 **Table 3. Applications of the emulsion diffusion method**

Encapsulated molecule	Polymer	Size	Zeta potential (mV)	Reference
Articaine	PCL	-	-	(Campos et al. 2013)
Omeprazole	Eudragit L 100-55	256.3-337.1 nm	8.92 - 16.53	(Hao et al. 2013)
Curcumin	polyurethane and polyurea	216-4901 nm	-	(Souguir et al. 2013)
Matricaria recutita L. extract	PEG-PBA-PEG	186-446 nm	-	(Esmacili et al. 2011)
Bovine serum albumin	Chitosan	81-98 μ m	-	(Karnchanajindanun et al. 2011)
Alendronate	PLGA	145 nm	-4.7	(Cohen-Sela et al. 2009)
An oligonucleotide	PLA	390 nm	-	(Delie et al. 2001)

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3.3.Simple Emulsion evaporation (SEE):



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Figure 3. Emulsion solvent evaporation (Pinto Reis et al. 2006)

321
 322 The SEE technique is widely used in the field of particulate carriers' development. This
 323 method was first developed by (Vanderhoff et al. 1979). It consists mainly on the formation of
 324 a simple emulsion followed by the evaporation of the organic solvent. Subsequent
 325 precipitation of the polymer allows the obtaining of the particles (Figure 3). Practically, for oil
 326 in water emulsion method, the polymer is dissolved in a volatile and non miscible organic
 327 solvent such as chloroform, ethylacetate or dichloromethane. This organic phase, in which the

328 drug and the polymer are dissolved, is then dispersed by high speed homogenization or by
 329 sonication in an aqueous phase containing a surfactant. Once an oil-in-water (o/w) emulsion is
 330 obtained, the evaporation of the organic solvent permits the precipitation of the polymer and
 331 thus, the formation of the particles. As it can be seen in Table 4, SEE is generally used for the
 332 encapsulation of hydrophobic drugs (O'Donnell & McGinity 1997). The evaporation of the
 333 organic solvent is obtained by moderately stirring the emulsion at room temperature or under
 334 high temperature and low pressure conditions. The obtained particles can be then harvested by
 335 ultracentrifugation or filtration then washed and lyophilized. Membrane technology was also
 336 used to prepare particles by the simple emulsion technique (Doan et al. 2011). Another
 337 alternative of the technique is the use of water in oil emulsion method that is suitable for the
 338 encapsulation of hydrophilic active molecules. Particulate carriers are obtained after
 339 evaporation of the water phase which causes the precipitation of the hydrophilic polymer
 340 (Banerjee et al. 2012). Parameters that have to be managed include organic phase to water
 341 phase ratio, nature of the surfactant and its concentration, stirring rate, polymer amount and
 342 evaporation rate. Decreasing the organic solvent volume resulted generally in a decrease of
 343 the particle size (Budhian et al. 2007). Particle size could also be decreased by increasing
 344 surfactant amount (Valot et al. 2009)(Manchanda et al. 2010)(Khaled et al. 2010)(Su et al.
 345 2009), increasing stirring rate (Su et al. 2009)(Lee et al. 2012)(Avachat et al. 2011)(Yadav &
 346 Sawant 2010) or increasing aqueous phase (Adibkia et al. 2011). However, an increase of
 347 polymer amount generally increases particles' size (Doan et al. 2011)(D'Aurizio et al.
 348 2011)(Adibkia et al. 2011)(Agnihotri & Vavia 2009). Table 4 shows the applications of the
 349 SEE technique in drug delivery. Polyesters are widely used for the encapsulation on
 350 hydrophobic drugs.

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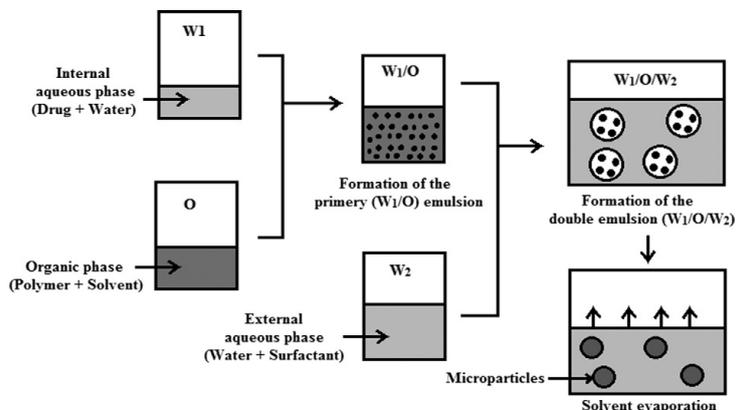
Table 4. Applications of the emulsion solvent evaporation technique

Encapsulated molecule	Polymer	Size	Zeta potential (mV)	Reference
Curcumin	PLGA and PLGA-PEG	161.9-152.4 nm	-	(Khalil et al. 2013)
Efavirenz	PCL and Eudragit® RS 100	83.4-219.5 nm	53	(Seremeta et al. 2013)
Human amylin	PCL	202 nm	-	(Guerreiro et al. 2012)
Azithromycin	PLGA	14.11-15.29 µm	-	(Li et al. 2012)
Teniposide	PLGA	113.9-135.4 nm	-36.6-(-23.1)	(Mo et al. 2012)
Camptothecin	PCL-PEG-PCL	4.2-5.4 µm	-	(Dai et al. 2011)
Naproxen	PLGA	352-824 µm	-	(Javadzadeh et al. 2010)
Doxorubicin	PLGA	137-164 nm	-12.3-(-9.9)	(Manchanda et al. 2010)
Dexamethasone	PLGA	5.18-7 µm	-	(Rawat & Burgess 2010)
Ibuprofen	Eudragit RSPO	14-51.1 µm	-	(Valot et al. 2009)

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354 **3.4.Double emulsion evaporation (DEE):**

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356

357 **Figure 5. Double emulsion solvent evaporation technique (Giri et al. 2013)**

358 Double emulsion technique is suitable for the encapsulation of hydrophilic molecules (See
 359 Table 5). Generally, the method consists on the dispersion of an aqueous phase in a non
 360 miscible organic solvent to form the first emulsion (W1/O). This dispersion is performed
 361 under high shear homogenization or low power sonication for a short time. This step is
 362 followed by the dispersion of the obtained emulsion in a second aqueous phase containing a
 363 hydrophilic emulsifier. Again, homogenization could be carried under high shear
 364 homogenization or with a sonication probe. When sonication is used, it must be performed at
 365 low power and within a short period of time to not break the first emulsion (Giri et al. 2013).
 366 After the formation of the multiple emulsion, evaporation of the volatile organic solvent under
 367 low pressure (by a rotary evaporator) or at ambient temperature allows the obtaining of the
 368 particulate carriers (Figure 4). There are other types of multiple emulsions like w/o/o or o/w/o
 369 (Giri et al. 2013). A lot of parameters may influence the properties of the obtained particles
 370 such as, relative phases' ratio (Khoee et al. 2012), amount of the polymer and its nature and
 371 molecular weight (Zambaux et al. 1998) (Péan et al. 1998) (Van de Ven et al. 2011), nature of
 372 the surfactants and their amounts (Zhao et al. 2007)(Khoee & Yaghoobian 2009)(Dhanaraju et
 373 al. 2004), homogenization speed (Eley & Mathew 2007)(Basarkar et al. 2007), the
 374 composition of the external phase (Péan et al. 1998) (Tse et al. 2009) and evaporation speed
 375 (Khoee et al. 2012). Operating conditions may also influence strongly encapsulation
 376 efficiency (Tse et al. 2009)(Billon et al. 2005)(Silva et al. 2013)(Zhou et al. 2013)(Karataş et
 377 al. 2009)(Hachicha et al. 2006)(Al-Kassas 2004)(Cun et al. 2011)(Gaignaux et al. 2012)(Cun
 378 et al. 2010). Membrane technique and microfluidic devices were also used to prepare
 379 particulate carriers by the DES method (Vladislavjević & Williams 2007)(van der Graaf et al.
 380 2005).

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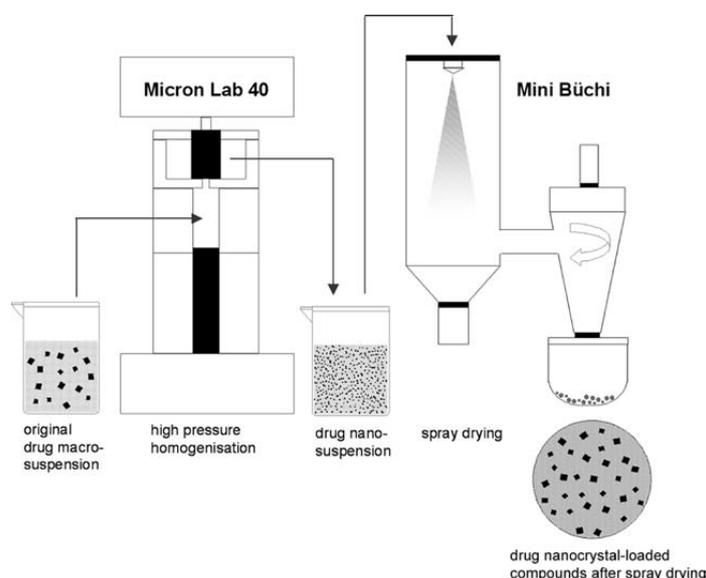
382 **Table 5. Applications of the double emulsion technique**

Encapsulated molecule	Polymer	Size	Zeta potential (mV)	Reference
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Vancomycin	PLGA	450-466 nm	-7.2-(-3.5)	(Zakeri-Milani et al. 2013)
Prostaglandin E1	PLGA	7-22.5 μ m	-	(Gupta & Ahsan 2011)
Deoxyribonuclease I	PLGA	190.4-349 nm	-	(Osman et al. 2011)
<i>S. equi</i> antigens	PCL	242.5-450.2 nm	-53.1-38.7	(Florindo et al. 2009)
Hepatitis B surface antigen	PLGA	1-5 μ m	0.51-14	(Thomas et al. 2009)
Plasmid DNA	PLGA	1.9-4.6 μ m	-24.6-(-22.9)	(Tse et al. 2009)

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384 **3.5.Spray drying:**



385

386 **Figure 4. The spray drying method** (Pinto Reis et al. 2006)

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388 Spray drying is a simple process which gained too much interest due to its cost-effectiveness
 389 and scalability (Sou et al. 2011). Practically, a polymer containing drug solution is atomized
 390 and sprayed into a drying chamber where droplets are dried by heated air. Reduction of
 391 droplets' size that follows atomization allows the obtaining of an enormous surface area
 392 between droplets and the drying gas. The subsequent precipitation of the polymer permits the
 393 encapsulation of the drug within the obtained particulate carriers. The evaporation of the
 394 solvent occurs within a very short period of time. Consequently, the materials never reach the
 395 inlet temperature of drying gas. This is very attractive for encapsulating heat-sensitive drug
 396 molecules like proteins (Cal & Sollohub 2010)(Sollohub & Cal 2010)(Prata et al. 2013).
 397 Many operating conditions could influence the properties of the obtained particles. Parameters
 398 to be controlled include the drying air temperature and humidity (Bruschi et al. 2003), the rate

399 and fluid dynamics of the air flow, the atomization process (Droplet size, spray rate, spray
400 mechanism) and the composition of ingredients and excipients in the feeding solution (Rattes
401 & Oliveira 2007). PLA (Baras et al. 2000)(Gander et al. 1996)(Sastre et al. 2007)(Muttill et al.
402 2007), PLGA (Wang & Wang 2002)(Mu & Feng 2001)(Castelli et al. 1998)(Bittner et al.
403 1999)(Prior et al. 2000)(Conti et al. 1997), PCL, methacrylate polymers (Esposito et al.
404 2002)(Año et al. 2011)(Cruz et al. 2010)(Hegazy et al. 2002)(Raffin et al. 2008) and chitosan
405 (He et al. 1999)(Giunchedi et al. 2002)(Cevher et al. 2006) are among the most used polymers
406 in spray-drying method. As Table 6 shows, the technique allowed the obtaining of mainly
407 microparticles bearing better drug solubility and sustained release.

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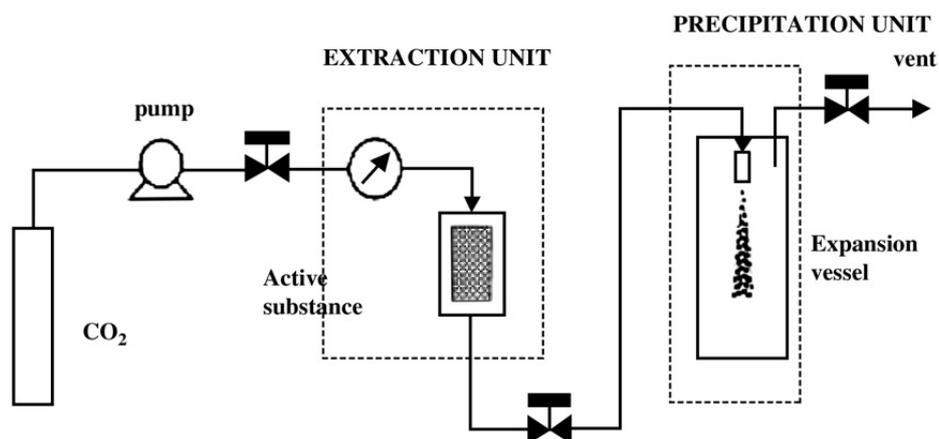
Table 6. Applications of the spray drying technique

Encapsulated molecule	Polymer	Size	Zeta potential (mV)	Reference
Nimodipine	PLGA	1.9-2.37 μm	-	(Bege et al. 2013)
Theophylline	Eudragit RS30D	< 60 μm	-	(Garekani et al. 2013)
Ofloxacin	PLA	2.6-4.9 μm	-	(Palazzo et al. 2013)
Sodium diclofenac	PGA-co-PDL PEG-PGA-co-PDL and mPEG-co-(PGA-co-PDL)	2.3 μm 3.9 μm 2.5 μm	-32.2 -29.9 -31.2	(Tawfeek 2013)
Sodium fluoride	Chitosan	3.4-5.3 μm	-	(Keegan et al. 2012)
Plasmid	Chitosan	2.5-11.7 μm	-	(Mohajel et al. 2012)
Heparin	PLGA	2.5-3.8 μm	-63.5 - (-28.2)	(Yildiz et al. 2012)
Alendronate	Eudragit® S100	13.8 μm	-	(Cruz et al. 2010)
Zolmitriptan	Chitosan glutamate and Chitosan base	2.6-9.4 μm	-	(Alhalaweh et al. 2009)
Triamcinolone	PLGA	0.5-1.5 μm	-	(da Silva et al. 2009)
Acyclovir	Chitosan	18.7-34.9 μm	-	(Stulzer et al. 2009)

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3.6. Supercritical fluid technology (SFT):



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Figure 6. Schematic presentation of the experimental set up for the RESS process (Byrappa et al. 2008)

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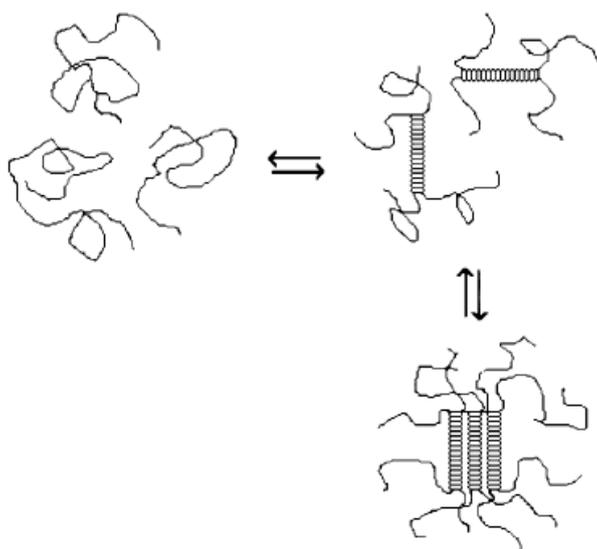
In the recent years, novel particle formation techniques using supercritical fluids (SCF) have been developed in order to overcome some of the disadvantages of conventional techniques that are: (1) poor control of particle size and morphology; (2) degradation and lost of biological activity of thermo sensitive compounds; (3) low encapsulation efficiency and (4) low precipitation yield (Santos et al. 2013). Moreover, SFT present the main advantage of not requiring the use of toxic solvents. In fact, SCF based technologies have attracted enormous interest for the production of microparticles and nanoparticles (Table 7), since their emergence in the early 1990s (Sanli et al. 2012). The supercritical state is achieved when a substance is exposed to conditions above its critical pressure and temperature. In such conditions, the fluid will have liquid-like density and, thus, solvating properties that are similar to those of liquids and, at the same time, gas-like mass transfer properties. Carbon dioxide (CO₂) is the most commonly used critical fluid. In fact, CO₂ is nontoxic, nonflammable and easy recyclable. Moreover, CO₂ has moderate critical parameters of CO₂ (a critical pressure of 7.4 MPa and a critical temperature of 304.1 K) and low price and is highly available which makes it very attractive from an economical point of view and also for the processing of labile compounds (Elizondo et al. 2012). Supercritical fluid technology methods can be divided in four methods which are rapid expansion of supercritical solution (RESS), Particles from gas saturated solutions (PGSS), gas antisolvent (GAS) and supercritical antisolvent process (SAS). These methods depend on whether CO₂ was used as a solvent, a solute or an antisolvent. Figure 6 shows the experimental set up of the RESS technique. In the RESS technique, the drug and the polymer are first dissolved in supercritical CO₂ in high pressure chamber. The subsequent passing of the solution through a nozzle results in a rapid decrease of the pressure and thus, a precipitation of the drug particles embedded in the polymer matrix and their recovery in the extraction unit (Byrappa et al. 2008). A lot of parameters such as the density of the SCF (Pressure and temperature of supercritical fluid) (Kalani & Yunus 2012), flow rate of drug-polymer solution and/or CO₂ and formulation variables (Martin et al. 2002) could influence the size of the obtained particles. Table 7 shows that SFT was used for the processing of nanoparticles and microparticles mainly based on polyesters.

444

Table 7. Applications of the SCF technology

Encapsulated molecule	Polymer	Size	Zeta potential (mV)	Reference
Hydrocortisone acetate	PLGA	1-5 μm	-	(Falco et al. 2013)
17 α -methyltestosterone	PLA	5.4-20.5 μm	13.9 - 67.7	(Sacchetin et al. 2013)
Paracetamol	PLA	301-1461 nm	-	(Kalani & Yunus 2012)
5-fluorouracil	PLLA-PEG/PEG	175 nm	-	(Zhang et al. 2012)
Human growth hormone	PLGA	93 μm	-	(Jordan et al. 2010)
Azacytidine	PLA	2 μm	-	(Argemí et al. 2009)
Bovine serum albumin	PLA	2.5 μm	-	(Kang et al. 2009)
Retinyl palmitate	PLA	40-110nm	-	(Sane & Limtrakul 2009)
Indomethacin	PLA	2.35 μm	-	(Kang et al. 2008)

446

447 **3.7.Ionic gelation (IG):**

448

449 **Figure 7. Gelation mechanism of polysaccharides in water (Guenet 1992)**

450 IG method is used mainly with natural hydrophilic polymers to prepare particulate carriers.
 451 These polymers include gelatin, alginate, chitosan and agarose. IG has the advantage of not
 452 using organic solvents. The technique is based on the transition of the polymer from liquid

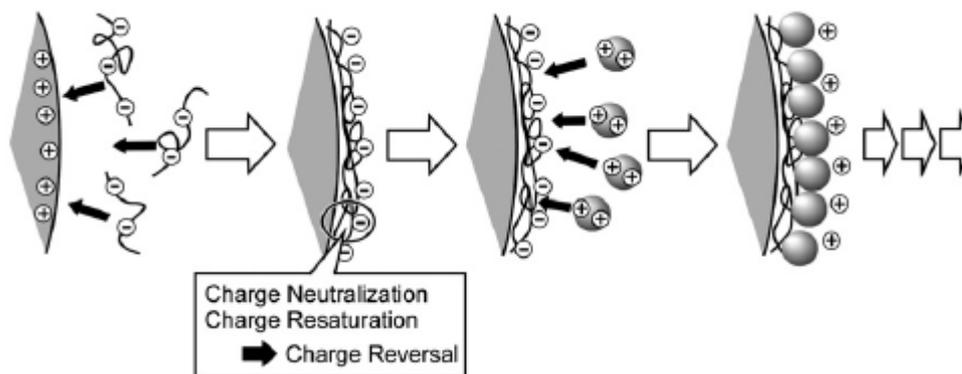
453 state to a gel (Figure 7). For instance, gelatin based particles are obtained after the hardening
 454 of the droplets of emulsified gelatin solution. The particles are obtained after cooling gelatin
 455 emulsion droplets below the gelation point in an ice bath. For alginate, however, particles are
 456 produced by drop-by-drop extrusion of the sodium alginate solution into the calcium chloride
 457 solution. Sodium alginate, in fact, is a water-soluble polymer that gels in the presence of
 458 multivalent cations such as calcium. Chitosan particles are prepared by spontaneous formation
 459 of complexes between the positively charged chitosan and polyanions (tripolyphosphate or
 460 gelatin) or by the gelation of a chitosan solution dispersed in an oil emulsion (Mahapatro &
 461 Singh 2011). Figure 7 illustrates the gelation mechanism of polysaccharides. At high
 462 temperatures, a random coil conformation is assumed. With decreasing temperature, the
 463 aggregation of double helices structure forms the physical junctions of gels (Rees & Welsh
 464 1977).

465 *Table 8. Some applications of the ionic gelation technique*

Encapsulated molecule	Polymer	Size	Zeta potential (mV)	Reference
Articaine hydrochloride	Alginate/chitosan	340-550 nm	-22 - (-19)	(de Melo et al. 2013)
TNF- α siRNA	trimethyl chitosan-cysteine	146.9 nm	25.9	(He et al. 2013)
Paclitaxel	O-carboxymethyl chitosan	130-180 nm	-30 - (-12)	(Maya et al. 2013)
pDNA	Chitosan	403-153 nm	46.2 - 56.9	(Cadete et al. 2012)
Gemcitabine	Chitosan	95 nm	-	(Derakhshandeh & Fathi 2012)
Dexamthasone sodium phosphate	Chitosan	256 – 350 nm	-	(Doustgani et al. 2012)
Itraconazole	Chitosan	190 - 240 nm	11.5 - 18.9	(Jafarinejad et al. 2012)
5-fluorouracil and leucovorin	Chitosan	40.7-97.4 nm	25.6 - 28.9	(Li et al. 2011)
Insulin	Chitosan and arabic gum	172-245 nm	35.7-43.4	(Avadi et al. 2010)
CKS9 peptide sequence	Chitosan	226.2 nm	-	(Yoo et al. 2010)

466

467 **3.8.Layer by layer:**



468

469 **Figure 8. The layer by layer technique based on electrostatic interaction** (Ariga et al. 2011)

470

471 Polyelectrolyte self assembly is also called layer-by-layer (LbL) assembly process. The
 472 earliest technology was based on the assembly of colloidal particles on a solid core (Iler
 473 1966). From the 1990s, applications were expanded. LbL allowed, in fact, the assembly of
 474 polyelectrolyte films using organic and biopolymers, proteins, peptides, polysaccharides and
 475 DNA (Powell et al. 2011). This approach was first developed by Sukhorukov *et al*
 476 (Sukhorukov et al. 1998). Polyelectrolytes are classified according to their origin. Standard
 477 synthetic polyelectrolytes include poly(styrene sulfonate) (PSS), poly
 478 (dimethyldiallylammonium chloride) (PDDA), poly(ethylenimine) (PEI), poly(N-isopropyl
 479 acrylamide) (PNIPAM), poly(acrylic acid) (PAA), poly (methacrylic acid) (PMA), poly(vinyl
 480 sulfate) (PVS) and poly(allylamine) (PAH). Natural polyelectrolytes include nucleic acids,
 481 proteins and polysaccharides such as, alginic acid, chondroitin sulfate, DNA, heparin,
 482 chitosan, cellulose sulfate, dextran sulfate and carboxymethylcellulose (de Villiers et al.
 483 2011). The obtained particles are vesicular and are called polyelectrolyte capsules. Assembly
 484 process is based on irreversible electrostatic attraction that leads to polyelectrolyte adsorption
 485 at supersaturating polyelectrolyte concentrations. Other interactions such as, hydrogen bonds,
 486 hydrophobic interactions and Van der Waals forces were also described (de Villiers et al.
 487 2011). A colloidal template that serves to the adsorption of the polyelectrolyte is also needed.
 488 The commonly used cores for the formulated particles are derived from stabilized colloidal
 489 dispersions of charged silica, charged poly(styrene) spheres, metal oxides, polyoxometalates
 490 and conducting liquid crystalline polymers. Carrier systems can be functionalized with
 491 stimuli-responsive components that respond to temperature, pH and ionic strength. The
 492 polymers/colloids used in the polyelectrolytes self -assembly technique can also be
 493 functionalized to alter its properties preceding layer by layer assembly. Experimental
 494 parameters that have to be managed include coating material concentration, ion concentration
 495 and the pH of the medium (Vergaro et al. 2011). Polymer assembly occurs after incubation of
 496 the template in the polymer solution or by decreasing polymer solubility by drop-wise
 497 addition of a miscible solvent (Radtchenko et al. 2002). This procedure could be repeated
 498 with a second polymer to allow sequential deposition of multiple polymer layers (Figure 8).
 499 The polyelectrolytes self-assembly presents advantages over a lot of conventional coating
 500 methods: (1) the simplicity of the process and equipment; (2) its suitability to coating most

501 surfaces; (3) the availability of an abundance of natural and synthetic colloids; (4) the flexible
 502 application to objects with irregular shapes and sizes; (5) the formation of stabilizing coats
 503 and (6) control over the required multilayer thickness (de Villiers et al. 2011).

504

505 **Table 9. Applications of the layer by layer technique**

Active	Polyelectrolytes	Size	Zeta potential (mV)	References
Kaempferol	Sodium Alginate and protamine sulfate	161 nm	- 8.9	(Kumar et al. 2012)
Designed peptide DP-2015	poly-l-glutamic acid and poly-l-lysine	-	-	(Powell et al. 2011)
5-fluorouracil	Poly(L-glutamic acid) and chitosan	1 μ m	25-40	(Yan et al. 2011)
Plasmid DNA	plasmid DNA and reducible hyperbranched poly(amidoamine) or polyethylenimine	-	-	(Blacklock et al. 2009)
Artemisinin	Alginate, gelatin and chitosan	806 nm	-33	(Chen et al. 2009)
Insulin	glucose oxidase and catalase	6 μ m	-	(Qi et al. 2009)
Heparin	poly(styrene sulfonate) and chitosan	1 μ m	-10.4	(Shao et al. 2009)
Acyclovir	Poly(vinyl galactose ester-co-methacryloxyethyl trimethylammonium chloride) and poly(sodium 4-styrenesulfonate)	-	-	(Zhang et al. 2008a)
Propranolol hydrochloride	Poly(vinyl galactose ester-co-methacryloxyethyl trimethylammonium chloride) and Poly(sodium 4-styrenesulfonate)	5-15.6 μ m	-	(Zhang et al. 2008b)

506

507 **Conclusion:**

508 Encapsulation of active molecules is a crucial approach that has been widely used for many
 509 biomedical applications. It permits enhancement of bioavailability of molecules, sustained
 510 delivery, passive or active targeting and decrease of toxicity and side effects. These
 511 formulations can render some active molecules more suitable for a specific route such as the
 512 delivery of protein by the oral route or the delivery of some drugs via the blood brain barrier.
 513 Thus, they enhance efficiency, patient compliance and allow successful management of
 514 diseases. Many biodegradable and biocompatible polymers were investigated. The choice of
 515 the technique and the suitable polymer is a crucial step. It depends on the physicochemical

516 properties of the drug to be encapsulated. The management of operating conditions is also a
517 hard task to monitor particles' properties and to enhance drug loading. Recent research works
518 are focusing on active targeting by the coating the carriers by biomolecules that specifically
519 recognize a well-defined cell receptor. One can also notice a shift for more 'intelligent' drug
520 delivery systems. Responsive materials, for example, react to a specific physiological
521 stimulus such as a variation of pH to release the encapsulated drug. Other thermo-sensitive
522 materials deliver drugs at a specific temperature. It can be noted also that more attention is
523 paid to safer methods that avoid the use of organic solvents (RESS) or to techniques that
524 provide better reproducibility and easy scalability (microfluidics and membrane
525 emulsification technology), which could be attractive for industrial processing.

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