



**HAL**  
open science

## Encapsulation methods of active molecules for drug delivery

Narimane Lammari, Mohamad Tarhini, Karim Miladi, Ouahida Louaer, Abdeslam Hassen Meniai, Souad Sfar, Hatem Fessi, Abdelhamid Elaïssari

### ► To cite this version:

Narimane Lammari, Mohamad Tarhini, Karim Miladi, Ouahida Louaer, Abdeslam Hassen Meniai, et al.. Encapsulation methods of active molecules for drug delivery. Eric Chappel. Drug Delivery Devices and Therapeutic Systems, Elsevier, pp.289-306, 2021, 978-0-12-819838-4. <10.1016/B978-0-12-819838-4.00008-0>. <hal-03001404>

**HAL Id: hal-03001404**

**<https://hal.science/hal-03001404v1>**

Submitted on 8 Jun 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

# Encapsulation methods of active molecules for drug delivery

Narimane Lammari<sup>1,2</sup>, Mohamad tarhini<sup>1</sup>, Karim Miladi<sup>3,4</sup>, Wahida Louaer<sup>2</sup>, Abdeslam Hassen Meniai<sup>2</sup>, Souad Sfar<sup>3</sup>, Hatem Fessi<sup>1</sup>, Abdelhamid Elaissari<sup>1</sup>

<sup>1</sup> Univ Lyon, University Claude Bernard Lyon-1, CNRS, LAGEP-UMR 5007, F-69622 Lyon, France

<sup>2</sup> Environmental Process Engineering Laboratory, University Constantine 3, Salah Boubnider, Constantine, Algeria.

<sup>3</sup> University of Monastir, Laboratoire de pharmacie galénique, Rue Avicenne, 5000 Monastir, Tunisia

<sup>4</sup> Société Des Industries Pharmaceutiques de Tunisie SIPHAT, 2013 Ben Arous, Tunisia

## OUTLINE

### Abstract

#### 1. Introduction

#### 2. Polymer-based nanoparticles

##### 2.1 Nanoprecipitation

##### 2.2. Simple emulsion evaporation

##### 2.3. Double emulsion evaporation

##### 2.4. Ionic gelation

##### 2.5. Supercritical fluid method

#### 3. Liposomes

##### 3.1. Hydration of a Thin Lipid Film

##### 3.2. Detergent Surfactant Dialysis

##### Solvent Injection Technique

##### Reverse-Phase Evaporation (REV) Technique

##### Membrane contactor technology

#### 4. Solid lipid nanoparticles

##### 4.1. High pressure homogenization

##### 4.2. Microemulsion

##### 4.3. Emulsion methods

#### 5. Therapeutic applications

#### 6. Conclusion

## 43 **Abstract**

44           Recent years have witnessed the emergence of nanotechnology in the medicinal field  
45 in order to improve existing treatments and develop novel and efficient therapies.  
46 Nanostructured systems have attracted unprecedented interest in drug delivery due to their  
47 ability to overcome difficulties linked to conventional drug delivery systems. Nanocarriers  
48 increase drug solubility and permeability, improve bioavailability, reduce side effects and  
49 enhance the therapeutic efficiency, whilst providing a preferential accumulation of active  
50 molecules at specific tissue sites or cells. The present chapter highlights the different  
51 elaboration processes leading to the development of two main groups of organic nanocarriers;  
52 lipid based-nanocarriers (including liposomes and solid lipid nanoparticles) and polymer  
53 based-nanocarriers (including polymeric nanoparticles). These carriers are used to encapsulate  
54 and to deliver active molecules or in some cases, for in vitro diagnosis and more recently in  
55 theranostics applications.

56 **Keywords:** nanocarriers, polymeric nanoparticle, liposome, solid lipid nanoparticle, drug  
57 delivery.

58

## 59 **1. Introduction**

60           Over the past few decades, enormous efforts have been devoted to developing  
61 nanotechnology as a novel platform to bypass most common hurdles encountered in  
62 traditional drug delivery such as poor stability, low bioavailability, poor solubility and the  
63 bitter taste of active agents [1]. Nanotechnology, a buzzword of this era, has transformed the  
64 face of research in numerous sectors, such as textiles [2], electronic engineering [3],  
65 agriculture [4], food [5] and pharmaceutical/biomedical fields [6], [7]. The application of  
66 nanotechnology for diagnosis, treatment, monitoring, and control of biological systems  
67 promotes the concept of nanomedicine, an extensively studied field, in which many colloidal  
68 drug carriers have been designed, in particular, nanoparticles [6], [8], [9]. Nanoparticles (NPs)  
69 are nano-sized structures dedicated to: i) carry the pharmaceutical agent to a specific tissue, ii)  
70 protect the drug from premature degradation, iii) lower the required dose for effective therapy,  
71 iv) minimize side effects and thereby v) increase the safety profile and therapeutic index of  
72 drugs [10]. Moreover, NPs are employed as an approach to increase the bioavailability of  
73 pharmaceutical ingredients by improving the cellular uptake, especially in cancer treatment.  
74 For instance, doxorubicin, a well-known anticancer drug, suffers from its poor

75 pharmacokinetics behavior including poor bioavailability after oral administration. Khdair et  
76 al. displayed that encapsulating doxorubicin in chitosan-based-NPs enhances its uptake by  
77 MCF-7 and Caco-II tumor cell lines [11]. Regarding the cutaneous administration, NPs  
78 enhances the skin penetration of drugs. A recent study revealed that the encapsulation of  
79 psoralen, widely used for psoriasis treatment, in liposomal carriers, increases the skin  
80 permeation by 5 fold and reduced the cytokine levels of psoriasis [12]. Other drugs like  
81 docetaxel suffer from their low aqueous solubility which hinders their clinical uses. The  
82 nanoencapsulation could also hinder the low aqueous solubility. Qureshi et al. demonstrated  
83 that the incorporation of docetaxel in lipid nanocarriers leads to a 686 times increase in water  
84 solubility [13].

85         Depending on the preparation methods, nanocarriers can be broadly divided into two  
86 main categories: polymer-based nanocarriers and lipid-based nanocarriers [10]. Amongst the  
87 several nanoparticulate systems investigated in drug delivery, polymeric nanoparticles  
88 (pNPs), liposomes and solid lipid nanoparticles (SLNs) have received much attention [14]–  
89 [19]. In this context, this chapter highlights the recent development of nanocarrier systems for  
90 drug delivery with a focus on the principal properties and preparation methods of the main  
91 polymer based-nanocarriers (polymeric nanoparticles) and lipid based-nanocarriers (such as  
92 liposomes and solid lipid nanoparticles). Furthermore, the current status of their therapeutic  
93 applications is also presented and shortly discussed.

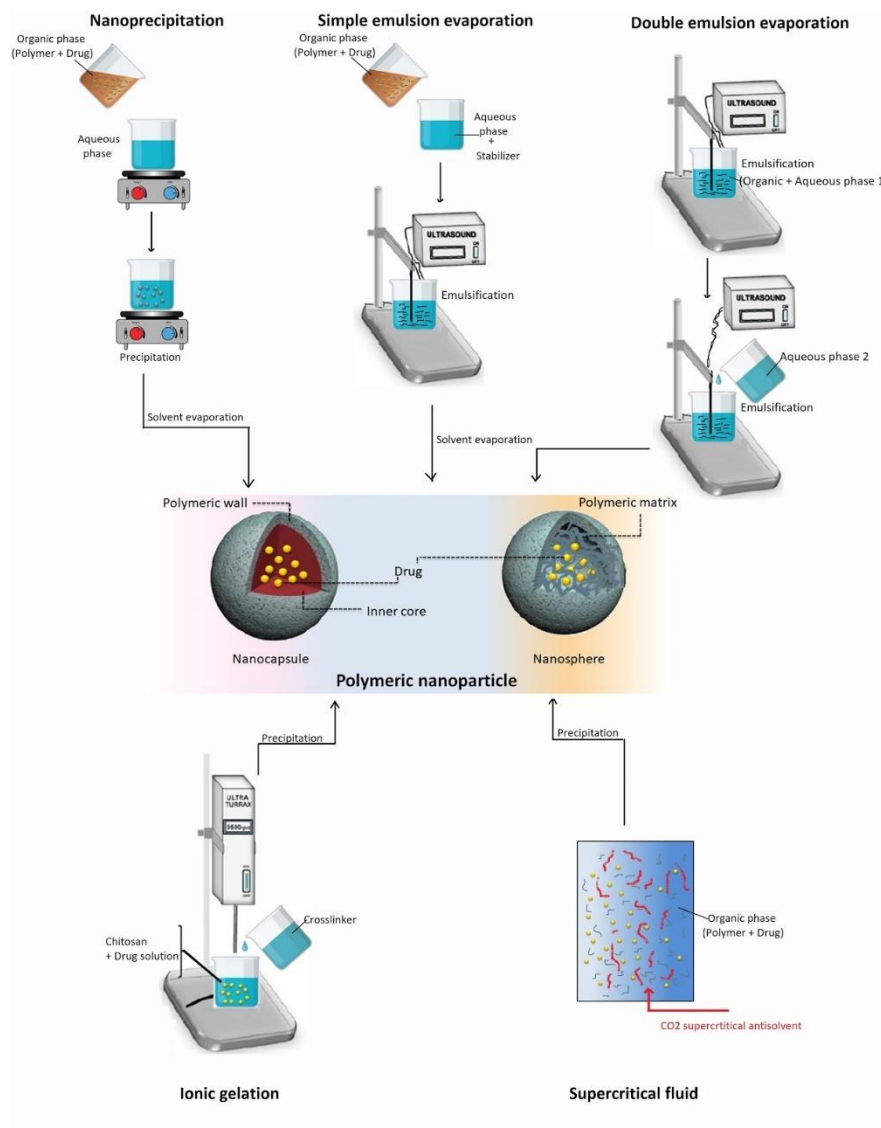
94

## 95         **2. Polymer-based nanoparticles**

96         During the last decades, polymeric nanoparticles have drawn tremendous attention  
97 owing to their peculiar characteristics and behaviours arising from their small size [20]. As  
98 demonstrated by different authors, these nanoparticulate systems show prospects for a wide  
99 range of applications due to their substantial benefits including upraised drug stability against  
100 photo- or chemical degradation, controlled drug release, increased drug-tissue interaction and  
101 consequently decreased adverse effects and improved therapeutic index [14], [21]–[23].  
102 Polymer-based nanoparticles are spherical in shape with a size range ranging from 10 to 1000  
103 nm. They can exist in two different forms, a polymeric layer surrounding a hollow core  
104 (nanocapsules), or a polymeric matrix extended from the core to the surface (nanospheres).  
105 The localization of the active molecule within these two forms depends on its chemical  
106 structure. In some cases, the drug can also be adsorbed or grafted onto the surface of the

107 particles [14], [24], [25]. Based on the origin of the polymer intended for NPs formulation,  
 108 two types are used: natural and synthetic polymers. Their main features are their  
 109 biodegradability and biocompatibility [26]. The most widely explored natural polymers are  
 110 chitosan, alginate and proteins such as albumin [27]. Amongst the various synthetic polymers,  
 111 polylactide–polyglycolide, polylactide, polycaprolactones, and polyacrylates have been  
 112 extensively used [28]. For the preparation of polymer-based particles, various methods have  
 113 been developed. The choice of the appropriate method depends on many factors such as  
 114 solubility of the drug in water and organic solvents, physicochemical properties of the  
 115 polymer and the target carrier specifications (i.e., size, size distribution, surface charge nature,  
 116 surface porosity, etc...) [20], [29]. The most commonly reported processes used for polymer  
 117 particles formulations are shown in Figure 1.

118



119

120

121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154

**Figure 1. Schematic illustration of nanoprecipitation, simple emulsion evaporation, and double emulsion evaporation processes.**

**2.1. Nanoprecipitation method**

Nanoprecipitation is a one-step process allowing the instantaneous and reproducible generation of narrow distribution of submicron particles[1]. It was first reported by Fessi et al. [30]. In this process, an organic solution containing a non-water-soluble polymer (solvent phase) is mixed with water (non-solvent phase). It is interesting to notice that both phases are miscible, and the mixture of the two phases becomes a bad solvent of the selected polymer leading to its precipitation via an instantaneous solvent diffusion mechanism [31]. For nanocapsules preparation, the same process is used except for adding oil to the organic phase in order to form an inner oily core [32]. The benefits of the nanoprecipitation technique include facility, rapidity, reproducibility, and scalability [33], [34]. Moreover, in this technique, the use of a stabilizer, in the case of charged polymer, or high production energy is avoided [35]. The main drawback of this method is low loading efficiency for hydrophilic drugs due to the hydrophobicity of a nanoparticle matrix [31]. Nonetheless, several strategies have been asserted to enhance the loading of these molecules [36].

**2.2. Simple emulsion evaporation method**

A simple emulsification evaporation method has been developed by Vanderhoff et al. to design polymeric nanoparticles [37]. In this process, the polymer and the drug are first dissolved in a volatile water-immiscible organic solvent. Ethyl acetate, owing to its better toxicological profile, has been widely used as a solvent instead of chloroform and dichloromethane [38]. The organic polymer solution is emulsified with an aqueous phase containing a suitable stabilizer under high shear stress (e.g. by homogenization or ultrasonication) [31]. The organic solvent is then evaporated by continuous stirring at room temperature or under reduced pressure leading to polymer precipitation and nanoparticle formation. The benefits of using this encapsulation method are high encapsulation efficiency of hydrophobic drugs, easy to process and good reproducibility. However, some disadvantages are related to this process; in particular, the poor encapsulation efficiency of hydrophilic drugs, the possible coalescence of droplets during evaporation which may lead to polydisperse polymer particles and the need for a high shear process in order to obtain submicron size with a narrow size distribution [1], [20].

### 155        **2.3. Double emulsion evaporation method**

156            The double emulsification evaporation method has been proposed as an alternative to  
157 nanoprecipitation and simple emulsification evaporation methods in term of encapsulation of  
158 hydrophilic drugs [39]. For instance, this technique, consisting of two-step emulsification, can  
159 encapsulate both hydrophobic and hydrophilic drugs because of the presence of several water  
160 and oil layers [40]. In the first step, the water-in-oil emulsion is formed after the  
161 homogenization of an aqueous phase (W1) containing the hydrophilic drug with an oily phase  
162 (O) that is generally a polymer solution dissolved in an organic solvent containing the  
163 necessary hydrophobic drug. The second step is the emulsification of the first W1/O emulsion  
164 in another aqueous phase (W2) containing an appropriate stabilizer, under high shear  
165 homogenization or low power sonication to form a double emulsion (W1/O/W2). Although  
166 this method can encapsulate both hydrophilic and hydrophobic drugs, it presents several  
167 drawbacks such as: low colloidal stability of the resulting particles, high shear stirring that  
168 may induce emulsion fragmentation, foam formation, and above-micron size polydisperse  
169 particles [1].

### 170        **2.4. Ionic gelation**

171            The ionic gelation method has been developed by Calvo et al. as a novel approach that  
172 avoids harmful organic solvents or high shear forces [41]. Among the different natural  
173 polysaccharides such as chitosan, some polyelectrolytes and alginates are widely used in the  
174 ionic gelation based process. These polyelectrolytes can be crosslinked by electrostatic  
175 interaction with an added oppositely charged molecules or macromolecules that can  
176 ultimately lead to ionic gelation and therefore to polysaccharide particles formation [42]. The  
177 ionic gelation consists of the transition from a liquid to gel state upon complexation between  
178 the positively charged amino group of chitosan and the negatively charged tripolyphosphate  
179 compound widely used as a polyanion crosslinker leading generally to submicron particles  
180 [43]–[45]. The main benefits of this method are in particular the use of aqueous solvents  
181 instead of organic solvents. Moreover, ionic gelation is simple, reproducible and a scalable  
182 process [46], [47].

### 183        **2.5. Supercritical fluid method**

184            All the above methods often involve the use of toxic solvents and / or surfactants that  
185 are dangerous to the environment as well as to physiological systems [48]. Consequently,  
186 current research has been directed to explore safer techniques to develop carriers of ....

189 Supercritical fluids have fascinated the interest of many researchers as they are  
190 environmentally friendly solvents [49]. Supercritical CO<sub>2</sub> is the most frequently used  
191 supercritical fluid due to its low price, abundance, non-flammability and non-toxicity. In the  
192 supercritical antisolvent process, the drug and the polymer are dissolved in a liquid solvent  
193 such as methanol that is totally miscible with the supercritical fluid. A supercritical  
194 antisolvent, A supercritical antisolvent is then added to the solution in a closed chamber, at  
195 ambient pressure. The insolubility of the solute in the fluid results in the instant precipitation  
196 of the solute, leading to particles formation [15]. Despite the advantage of using  
197 environmentally safe materials, some drawbacks are linked to this method since it requires  
198 special equipment and is very expensive to be developed as a routine technique [50].

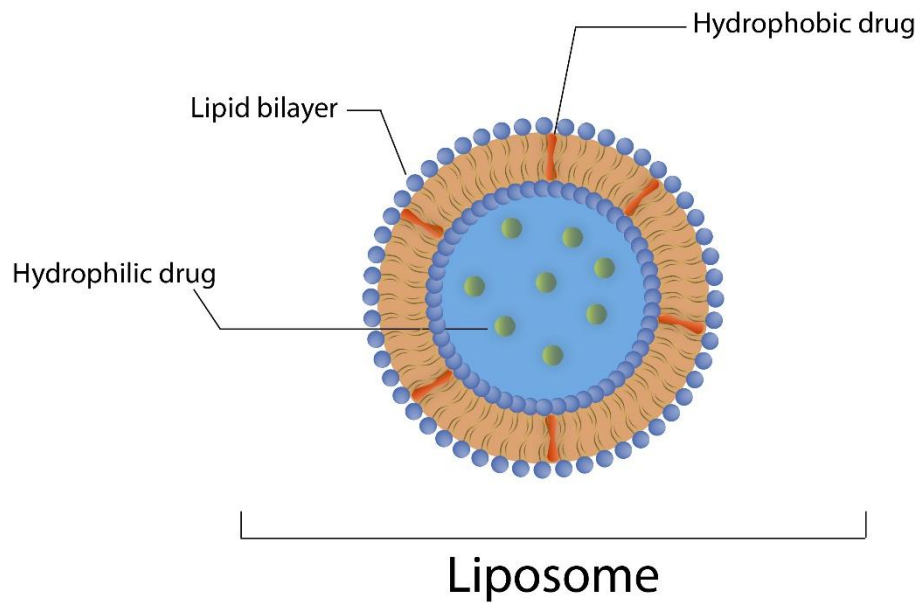
199

### 200 **3. Liposomes**

201 Liposomes were first described by Alec Bangham in 1961 [51], [52]. Liposomes are vesicles  
202 which are made of one or more lipid bilayers. They can be classified into 3 categories: small  
203 unilamellar vesicles (SUV), large unilamellar vesicles (LUV) and multilamellar vesicles  
204 (MLV). Liposomes can also be classified according to their surface charge. In fact, they can  
205 be non-charged (zwitterionic), cationic or anionic.

206 The interest of liposomes is related to their ability to contain hydrophilic molecules in their  
207 aqueous phase and lipophilic molecules in their lipid bilayers as illustrated in Figure 2 [53].  
208 Furthermore, liposomes bear a good cell affinity and biodegradability. Lipid bilayers are  
209 constructed of phosphatidylcholine and cholesterol. The latter ensures the physical stability of  
210 the bilayers.

211



212

**Figure 2. Liposomes containing hydrophilic and hydrophobic active drug.**

213

214

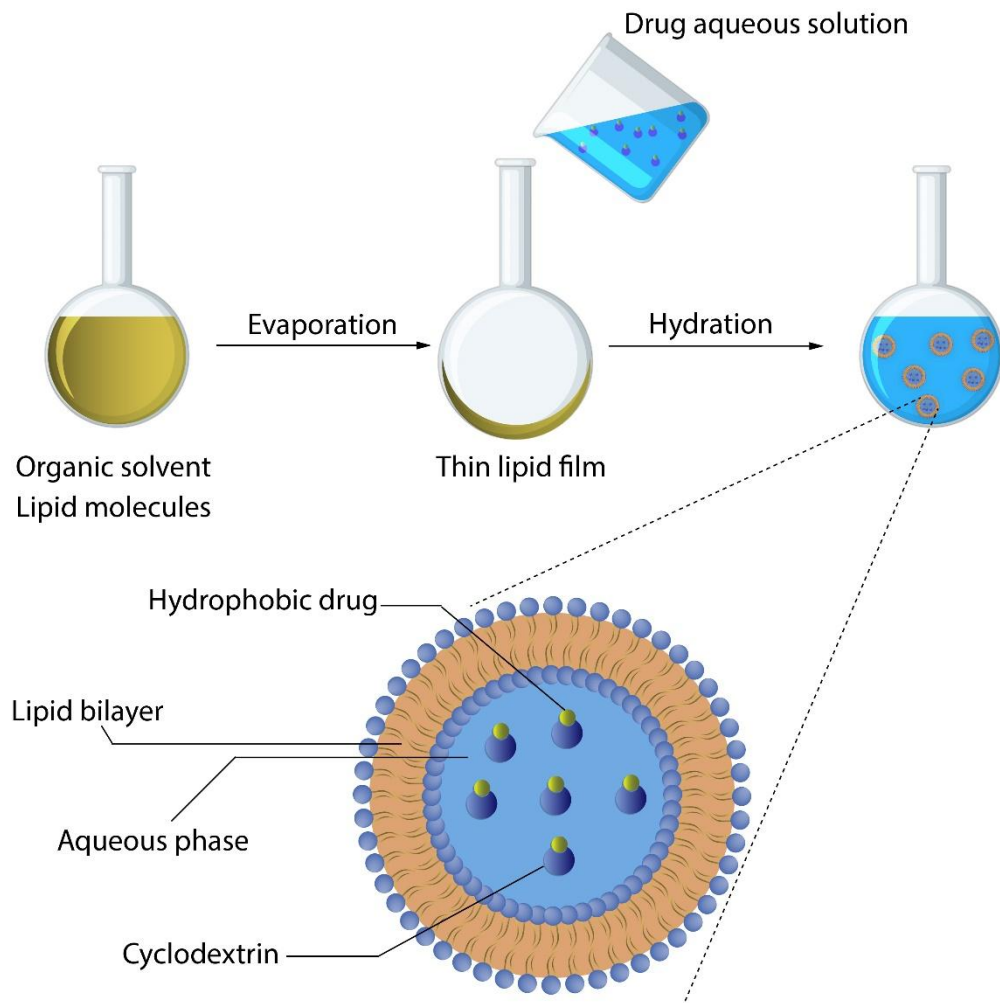
215

216

### **3.1. Hydration of a Thin Lipid Film**

217 Thin lipid film hydration is the first process used for liposomes preparation. This method  
218 consists of the dissolution of lipid ingredients in an organic solvent such as; ethanol, methanol  
219 or chloroform in a round-bottom flask [54]. Subsequent evaporation of the obtained  
220 phospholipids solution allows the formation of a lipid film. Its hydration by water or a buffer  
221 solution enables the formation of liposomes dispersion (see Figure 3). Sonication,  
222 homogenization or extrusion may also be performed to ensure size reduction and particles  
223 uniformity [55].

224



225

226 **Figure 3. Hydration of a thin lipid film (example of a hydrophobic drug incorporated in**  
 227 **cyclodextrins).**

228

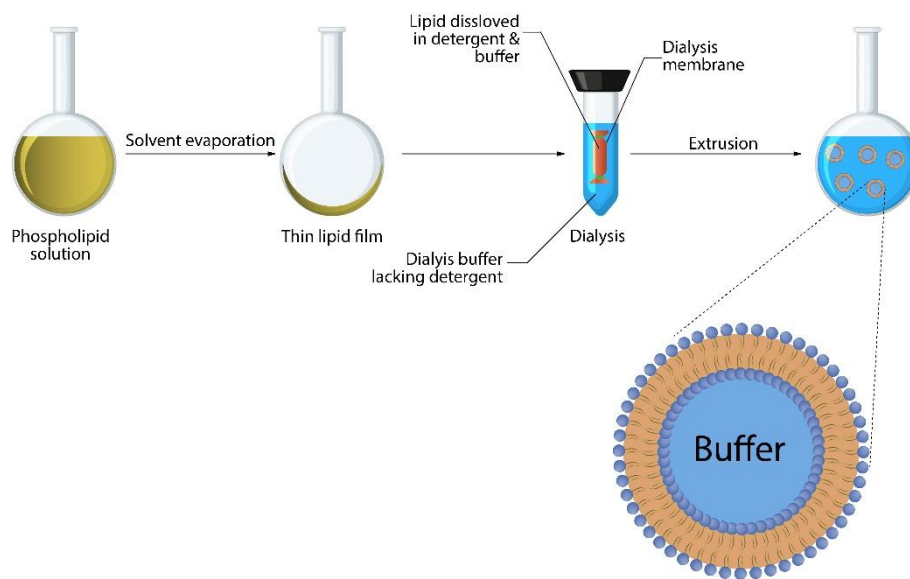
229

230

231 **3.2.Detergent Dialysis**

232 Detergents at their critical micelle concentrations (detergent concentration above which  
 233 micelles begin to form) can be used to solubilize lipids (see Figure 4). In the detergent dialysis  
 234 method, phospholipids are solubilized by detergent micelles in an aqueous phase. After  
 235 detergent removal by dialysis, phospholipid-rich micelles coalescence is obtained, and  
 236 liposomes are formed. Advantages of this technique include good reproducibility and size  
 237 uniformity. However, residual detergent retention represents the main drawback [55]. Dialysis  
 238 can be performed with a commercial device called LipoPrep (Diachema AG, Switzerland) can  
 239 also be obtained in dialysis bags engrossed in large detergent free buffers [56]. There are

240 other ways to using dialysis to remove detergent molecules such as chromatographic methods.  
241



242

243

**Figure 4. Detergent dialysis method.**

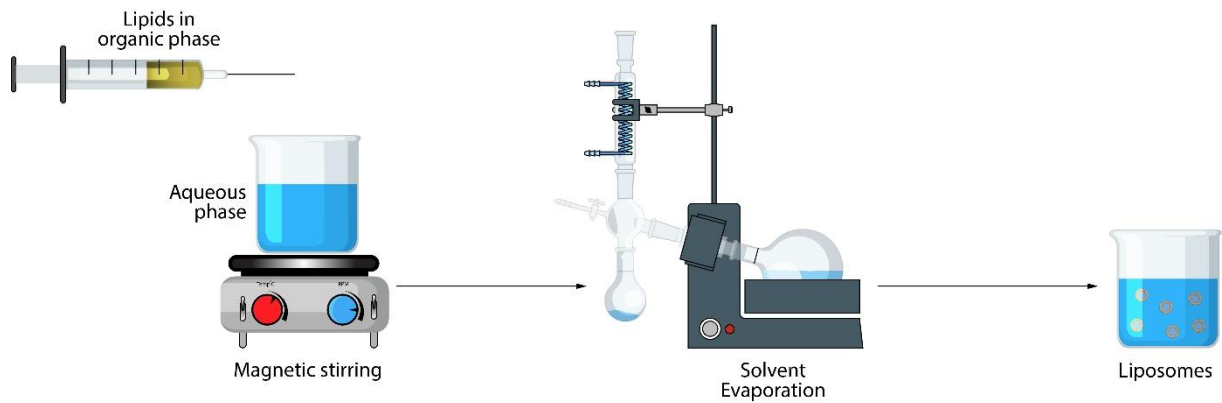
244

### 245 3.3.Solvent Injection Technique

246 In the solvent injection technique, phospholipids are dissolved in an organic solvent such as  
247 ethanol or ether, then, this solution is slowly injected into an aqueous buffer solution. SUV  
248 dispersion is then obtained. Self-assembly of lipids in the aqueous phase to form liposomes  
249 occurs following either ethanol dilution in water or ether evaporation (See Figure 5) [57].

250 The ethanol injection method was first described in 1973 [58]. The main advantage of this  
251 method is that narrow size distribution of submicron liposomes (generally under 100 nm)  
252 could be obtained without extrusion or sonication [59].

253 The ether injection method differs from the ethanol injection method since the ether is  
254 immiscible with the aqueous phase. The relevance of this method compared to the ethanol  
255 injection solvent removal from the product which allows the process to run for an extended  
256 period. A more prolonged process was shown to form concentrated liposomes suspension  
257 with high loading efficiency [59].



258

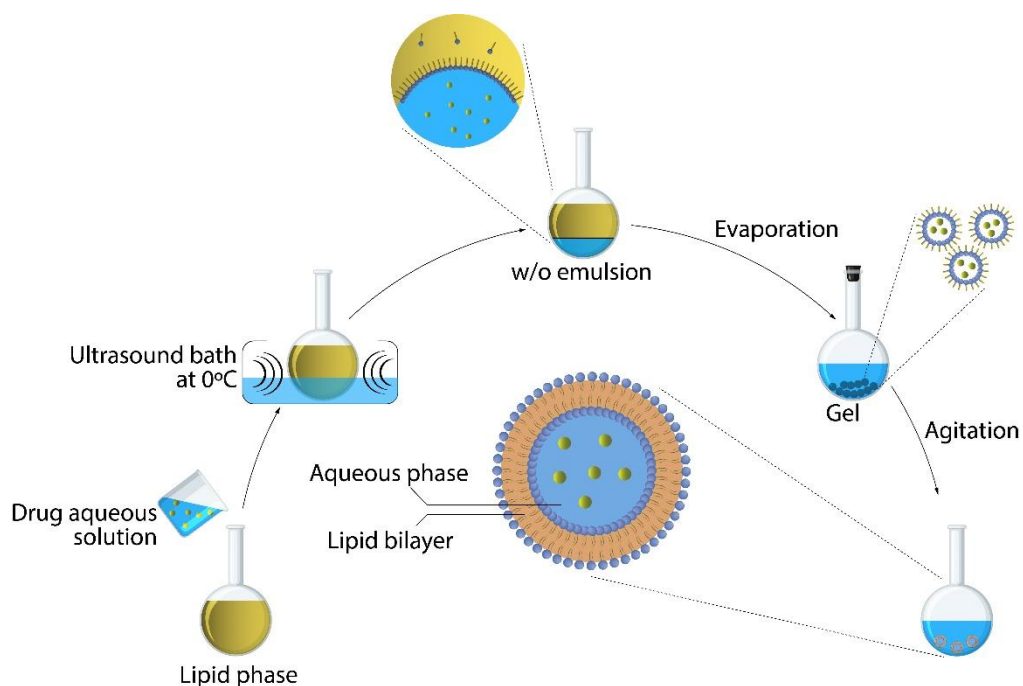
259

**Figure 5. Solvent injection technique.**

260

261 **3.4.Reverse-Phase Evaporation Technique**

262 The reverse phase evaporation method enables the preparation of liposomes with high  
 263 aqueous space-to-lipid ratio. This allows a large percentage of aqueous material to be loaded.  
 264 The technique is based on the creation of inverted micelles [56]. The latter are formed when  
 265 phospholipids solution in an organic phase is hydrated by the addition of water with vigorous  
 266 mixing. This results in the formation of a water-in-oil emulsion. Subsequent evaporation of  
 267 the organic phase results in the micelles transformation into a gel-like dispersion (Figure 6).  
 268 At some point, the gel state collapses and the excess of phospholipids in the environment  
 269 leads to an aqueous liposomes suspension containing both LUV and MLV [60].



270

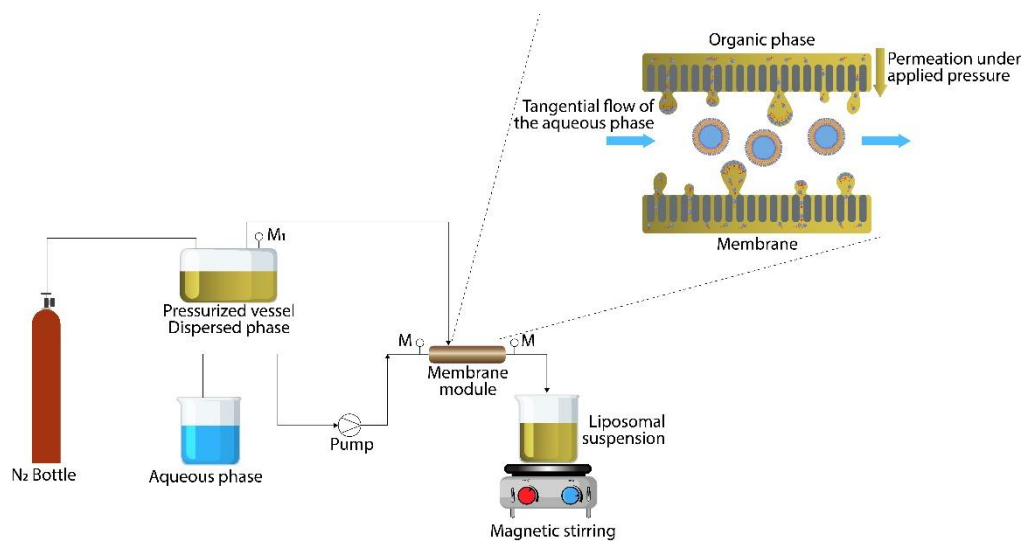
271

### Figure 6. Reverse phase evaporation technique

272

### 273 3.5.Membrane contactor technology:

274 Membrane contactors are used to mix two materials [61]. This property is used to enable the  
 275 mixing of the lipid and the water phase to obtain liposomes (see Figure 7). Jaafar-Maalej et al.  
 276 used a membrane contactor where phospholipid solution in ethanol was extruded into an  
 277 aqueous phase [62]. The obtained liposomes were prepared by a modified ethanol injection  
 278 method. In this study, a tubular Shirazu porous glass (SPG) membrane with a mean pore size  
 279 of 900 nm was used. Laouini et al., 2011, used polypropylene hollow fibers which allowed  
 280 access to larger membrane areas and uniform flows thus, improving efficiency [63]. Thi Thuy  
 281 Pham et al. reported the use of membrane contactor technology to produce liposomes on an  
 282 industrial scale. Their product could be obtained in a very reproducible manner [64].  
 283 Advantages of the membrane contactor technique include greater control of liposome size,  
 284 high encapsulation efficiency, continuous operation and scale-up of the process [55].



285

286 **Figure 7. Membrane contactor technique**

### 287 4. Solid lipid nanoparticles

288 Solid lipid nanoparticles (SLNs) are other lipid-based carriers that have emerged as a less  
 289 toxic, more biocompatible alternative for polymeric based nanoparticles. Moreover, it has  
 290 been claimed that SLNs actually unite the benefits of lipid emulsion systems, liposomes, and

291 polymeric nanoparticles, while sweeping away temporal and in vivo stability [65]. The  
292 general chemical composition of these particles are surfactants and sometimes co-surfactants  
293 and a lipid matrix that acquires a solid-state at physiological temperature. The lipid matrix of  
294 SLNs should be composed of lipids that have good biocompatibility and a melting point  
295 above body temperature. With these characteristics, the commonly used materials to structure  
296 the lipid core are fatty acids, fatty alcohols, waxes, and triglycerides. In fact, the crystal  
297 structure of the lipid core is critical for the feasibility of SLN systems since it may affect  
298 controlled drug release and colloidal stability of the dispersion. The formation of a solid core  
299 is determined by components ratio and the choice of the preparation method [66].

300 Different preparation methods were used in the literature to prepare SLNs such as high-  
301 pressure homogenization, microemulsion, solvent emulsification evaporation, and solvent  
302 emulsification diffusion [67]. These techniques are differentiated by the complexity of their  
303 execution and the characteristic of their final product [68].

304

#### 305 **4.1.High-pressure homogenization**

306 High-pressure homogenization (HPH) is widely used in the pharmaceutical industry since it is  
307 easy to scale-up and produce high-quality products with small particle size and higher  
308 homogeneity. HPH uses a sophisticated device (high-pressure homogenizer) that is able to  
309 push liquids through a narrow gap (micron size) with high pressure (from 100 to 2000 bar)  
310 creating an acceleration over a very short distance [69].

311 In brief, the lipid is heated at 5 to 10°C above its melting point, and the drug is dissolved  
312 within. After that, two different approaches can be undertaken One approach is hot  
313 homogenization, in which the drug-lipid melt is dispersed in a hot aqueous surfactant solution  
314 under stirring at the same temperature creating the pre-emulsion. Then, a hot oil-in-water  
315 (O/W) nanoemulsion is formed by homogenization using a piston-gap homogenizer. This  
316 nanoemulsion is then cooled to room temperature allowing the formation of lipid crystals  
317 creating SLNs [70].

318 Another approach is cold homogenization that is started with cooling down the drug-lipid  
319 melt allowing the formation of solid lipid microparticles (between 50 and 100 nm) that are  
320 then dispersed in a cold surfactant solution shaping a pre-suspension. This pre-suspension is  
321 on its turn and is strongly homogenized, breaking down the microparticles and forming SLNs.  
322 The cold HPH approach is used in the case of thermosensitive drugs where at cold conditions,

323 lipid melting is minimized and therefore prevents the diffusion of hydrophilic drugs into the  
324 water phase [71].

325

#### 326 **4.2. Microemulsion**

327 This method was first developed by Gasco [72]. It is based on the precipitation of lipid  
328 particles by diluting the system with water. Briefly, a microemulsion is formed by adding a  
329 mixture of water, surfactant, and co-surfactant to the lipid melt. Taking into account that the  
330 water mixtures should be heated to the same temperature as the lipid and added under mild  
331 stirring. The formed microemulsions are then diluted in a cold aqueous phase which causes  
332 their precipitation into SLNs.

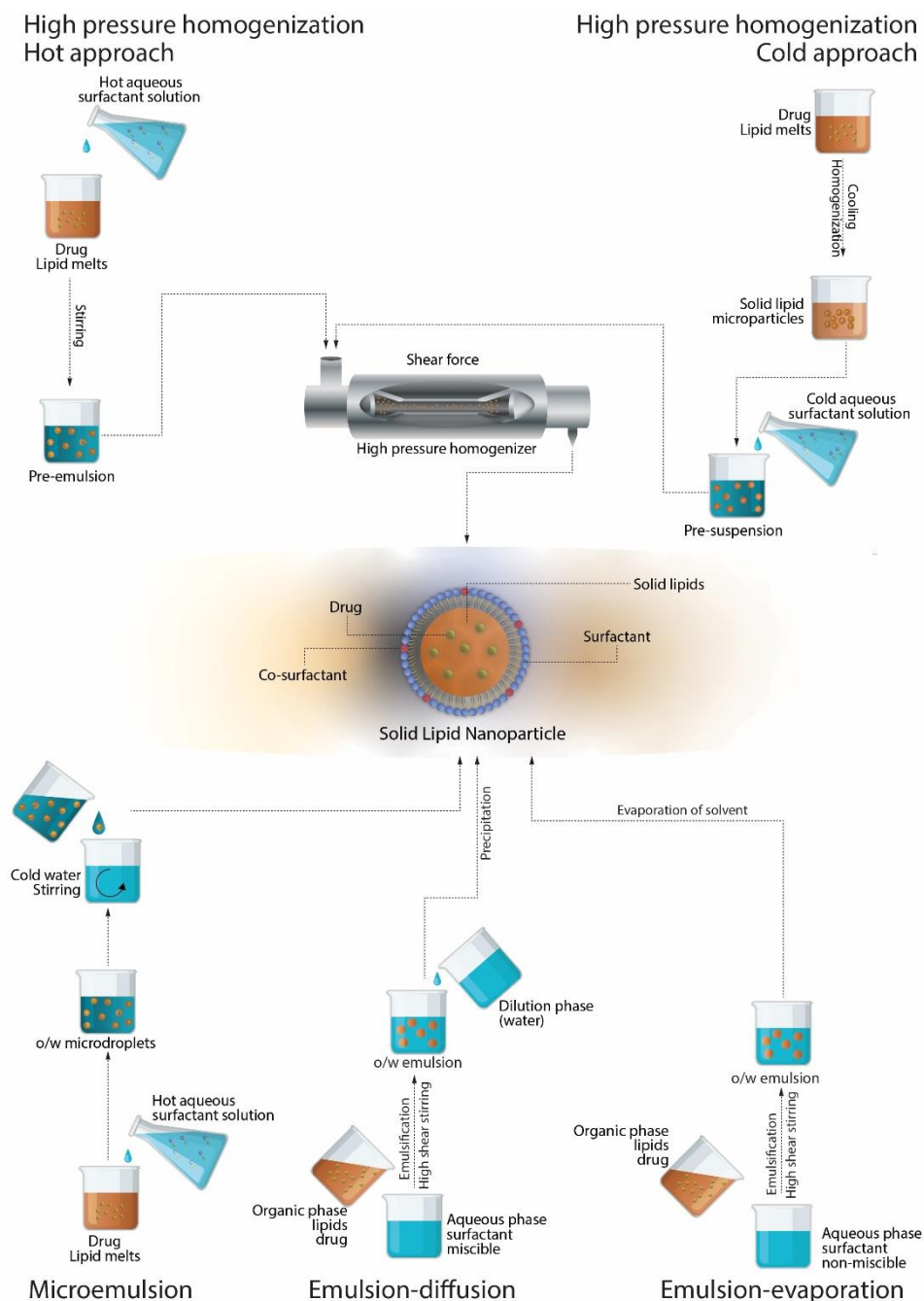
333 Different types of surfactants and co-surfactants were used in this method such as lecithin,  
334 biliary salts, and alcohols. In addition, it is important that during the precipitation step, mixing  
335 should be done by mild mechanical agitation to guarantee that the small size of the obtained  
336 SLNs is due to precipitation and not agitation. This method has the advantages of being a  
337 solvent-free process with gentle preparation conditions. Making it suitable for the  
338 encapsulation of various therapeutic peptides and active molecules [69].

#### 339 **4.3. Emulsion methods**

340 Emulsion-diffusion (ED) requires the use of three different liquid phases. The organic phase  
341 in which the lipids and the lipophilic drug are dissolved (solvent) and generally miscible with  
342 the aqueous phase. An aqueous phase containing a stabilizing agent (non-solvent) and a  
343 dilution phase that usually involves a large amount of water. Solvent and non-solvent phases  
344 are mutually saturated. The organic phase is emulsified in the water phase under high shear  
345 stirring. After that, the water dilution phase is subsequently added allowing the diffusion of  
346 the organic solvent to the outer water resulting in the precipitation of lipids and the formation  
347 of SLNs. The obtained SLNs by this method are diluted, therefore, a concentration step is  
348 followed by ultra-filtration or freeze-drying. The advantage of this technique is the avoidance  
349 of temperature use which reflects better stability of the system in general and the drug  
350 encapsulated in particular [73], [74].

351 Emulsion-evaporation (EE) is differentiated from ED by the fact that the non-solvent used  
352 should be immiscible with the solvent. In addition, it is critical that the evaporation  
353 temperature of the solvent is lower than the non-solvent. After the formation of a simple  
354 emulsion, the organic solvent is evaporated leading to the precipitation of the lipids in the

355 non-solvent phase and formation of nanoparticles that are stabilized instantaneously by  
 356 surfactants. This leads to the formation of O/W nanoemulsion and in some cases, a double  
 357 emulsion can be done leading to the formation of W/O formulations. A major drawback of EE  
 358 is the use of a water-immiscible solvent that can be harmful for human administration [69],  
 359 [75]. Figure 8 shows the different preparation techniques of solid lipid nanoparticles.



360

361

**Figure 8. Preparation methods of solid lipid nanoparticles**

362

## 5. Therapeutic applications:

363 Numerous active molecules have been encapsulated in nanomaterials to obtain various  
 364 therapeutic applications. This has led to the emergence of nanomedicine, which is the field  
 365 that combines nanotechnology with pharmaceutical and biomedical sciences. For instance,  
 366 polymeric nanoparticles represent the simplest form of soft materials used for nanomedicine  
 367 applications. This is due to their easy synthesis and wide biomedical applications. In fact, two  
 368 of the top 10 best-selling drugs in the US in 2013 were polymeric drugs (Copaxone® and  
 369 Neulasta®), [76], [77]. Liposomes also represent another feature of nanomedicine. Until  
 370 today, around 20 liposomal products have been approved by regulatory agencies, especially  
 371 for cancer management. Other therapeutic indications of liposome-based products include  
 372 antifungal and antibacterial drugs, analgesics, vaccines, and photodynamically active agents  
 373 [78]. In addition, lipid-based carriers have been evidenced to be attractive candidates for  
 374 active encapsulation. In fact, lipid materials could circumvent barriers associated with the oral  
 375 administration of poorly soluble drugs or drugs with intestinal permeability issues. Such  
 376 properties could be conferred by solid lipid nanoparticles or nanostructured lipid carrier [79].  
 377 The following Table 1 shows some examples of nanomedicine-based formulations.

378 **Table 1. Examples of therapeutic indications of liposome-based formulations**

Method	Materials	Encapsulated molecule	Size	Zeta	Application	Reference
<i>Polymer-based nanoparticles</i>						
Nanoprecipitation	Eudragit S100 and Hydroxypropylmethylcellulose phthalate	Pantoprazole	299 to 639 nm	-	Acid-related disorders and Helicobacter biliary infections	[80]
Nanoprecipitation	Poly-(D, L-lactic-co-glycolic acid)	Itraconazole	176 nm	-24 mV	Fungal infections	[81]
Nanoprecipitation	Poly-(D, L-lactic-co-glycolic acid)	Cisplatin	126 nm	-12 mV	Ovarian cancer	[82]
Simple emulsion	Poly-(D, L-lactic-co-glycolic acid) and Gly-L-Phe-DThr-Gly-L-Phe-L-	Curcumin	200-250 nm	-22 mV	Alzheimer's disease	[83]

	Leu-LSer(O-b-D-Glucose)-CONH <sub>2</sub> (g7)					
Simple emulsion	Poly-(D, L-lactic-co-glycolic acid) and carboxymethyl-poly(ethylene glycol)-b-poly(lactic acid)	Irinotecan derivative ( SN-38)	269-276 nm	-20(-26) mV	Cancer	[84]
Double emulsion	Poly-(D, L-lactic-co-glycolic acid)-PEG	Gemcitabine and betulinic acid	195 nm	-4 mV	Cancer	[85]
Double emulsion	Poly-(D, L-lactic-co-glycolic acid)	Doxorubicin	199 nm	-38 mV	Cancer	[86]
Double emulsion	Poly-(D, L-lactic-co-glycolic acid)	Frovatriptan Succinate	264 nm	-35 mV	Migraine	[87]
Ionic gelation	<i>N</i> -succinyl-chitosan and <i>N</i> -glutaryl-chitosan	Paclitaxel and docetaxel	300-350 nm	25-31 mV	Cancer	[88]
Ionic gelation	Chitosan	Letrozole	20-80 nm	-	Breast cancer	[89]
Ionic gelation	Chitosan	Carvedilol	102 nm	32 mV	Hypertension	[90]
Supercritical fluid method	Chitosan	Doxorubicin hydrochloride	120-250 nm	50 mV	Cancer	[91]
<b><i>Liposomes</i></b>						
Thin film hydration	Phosphatidylcholine, cholesterol, Dicylphosphate	5-FU	108 to 234 nm	-2.3 to -16.3 mV	Colorectal cancer	[92]
Thin film hydration	Pure phosphatidylcholine enriched phospholipids, cholesterol	Celecoxib	95 nm	- 42,8 mV	Inflammatory diseases	[93]
Modified thin-film hydration	Soybean phosphatidylcholine, cholesterol	Brinzolamide	96 nm	-1 mV	Glaucoma	[94]
Modified lipid hydration and extrusion	dipalmitoyl-glycero-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] and dipalmitoyl-glycero-phospho-(rac-glycerol)	Bevacizumab	100 - 200 nm	-	Ocular angiogenesis	[95]
Thin film hydration	Dipalmitoylphosphatidylcholine, distearoylphosphatidylethanolamine And Cholesterol	5-FU	174 nm	-	Cancer	[96]
Thin film hydration	Soybean phosphatidylcholine and cholesterol	Timolol maleate	129-437 nm	7-19 mV	Glaucoma	[97]
Thin film hydration	Hydrogenated soy phosphatidylcholine and cholesterol	Doxorubicin and Lovastatin	147 nm	-	Liver cancer	[98]
Thin film hydration	Di-(octadecenoyl)-glycero-phosphoethanolamine , dioleoyl-glycerotrimethylammonium propane (DOTAP), and	Si-RNA	206 – 360 nm	30 – 60 mV	Ocular keratitis	[99]

	distearoyl-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]					
Lipid film hydration	Distearoyl-glycero-phosphocholine	5-Fluorouracil and apigenin	105 nm	-3 mV	Colorectal cancer	[100]
Lipid film hydration	Dipalmitoyl-glycero-phosphocholine, distearoyl-glycero-phosphoethanolamine-[methoxy(polyethylene glycol)-2000], distearoyl-glycero-phosphoethanolamine-N-[maleimide(polyethylene glycol)-2000], and cholesterol	Gemcitabine and paclitaxel	168 nm	-	Pancreatic cancer	[101]
<b><i>Solid lipid nanoparticles</i></b>						
High pressure homogenization	Lipid 71 Compritol 88 ATO	Ezetimibe	156 nm	-20 mV	Hyperlipidemia	[102]
High pressure homogenization	Imwitor® 900K, Tagat® S and Sodium deoxycholate	Risperidone	114-195 nm	-	psychological disorders	[103]

379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399

## Conclusion

Nanomedicine offers an enormous outlook for upgrading current therapies and emerging new treatment tools for illness previously assumed difficult or impossible to treat. Nanostructured systems have shown exciting benefits due to their size and shape since they can reach areas which are inaccessible using other conventional drug delivery systems protect the drug molecules from premature degradation, sudden clearance, and toxic manifestations. Nanostructured systems can also deliver the drug to a specific tissue site or cell leading to increased drug amounts at a local site hence enhancing the therapeutic profile. In this chapter, we spotlight recent advances of both lipid and polymer based-nanocarriers such as liposomes, solid lipid nanoparticles and polymeric nanoparticles in the emergence of new concepts for the efficient transport of drug molecules. The first section of this review has provided information about the properties and recent developments in the synthesis of these nanosystems. Several methods have been explored for nanocarrier preparation, nonetheless, the choice of the appropriate approach is a crucial key to gain specific requirements. Additionally, this paper has reviewed current applications of these carriers. The discussed nanostructured systems provide interesting perspectives for applications in several fields such as drug and gene delivery, biomedical imaging, diagnosis, and theranostics. The specific functionalization of the carrier surface can enhance its biodistribution to target cells and limit its delivery into healthy ones. Consequently, engineering nanocarriers with specific surface

400 receptors can be considered to be the turning point leading, in the future to a potent use of  
401 these systems in large-scale therapeutic applications.

402

403

#### 404 **References:**

405

- 406 [1] B. Stella, A. Marengo, et S. Arpicco, « Nanoparticles: an overview of the preparation methods  
407 from preformed polymers », *Ist. Lomb. - Accad. Sci. E Lett. - Incontri Studio*, p. 11- 22, 2017.
- 408 [2] T. Harifi et M. Montazer, « Application of nanotechnology in sports clothing and flooring for  
409 enhanced sport activities, performance, efficiency and comfort: a review », *J. Ind. Textiles*, vol.  
410 46, n° 5, p. 1147- 1169, 2017.
- 411 [3] J. Lu, Z. Chen, Z. Ma, F. Pan, L. A. Curtiss, et K. Amine, « The role of nanotechnology in the  
412 development of battery materials for electric vehicles », *Nat. Nanotechnol.*, vol. 11, p. 1031–  
413 1038, 2016.
- 414 [4] R. Prasad, A. Bhattacharyya, et Q. D. Nguyen, « Nanotechnology in Sustainable Agriculture:  
415 Recent Developments, Challenges, and Perspectives », *Front. Microbiol.*, vol. 8, p. 1- 13, 2017.
- 416 [5] X. He et H.-M. Hwang, « Nanotechnology in food science: Functionality, applicability, and safety  
417 assessment », *J. Food Drug Anal.*, vol. 24, n° 4, p. 671- 681, 2016.
- 418 [6] A. P. Nikalje, « Nanotechnology and its Applications in Medicine », *Med. Chem.*, vol. 5, n° 2, p.  
419 81- 89, 2015.
- 420 [7] C. Enrico, « Chapter 3 - Nanotechnology-Based Drug Delivery of Natural Compounds and  
421 Phytochemicals for the Treatment of Cancer and Other Diseases », *Stud. Nat. Prod. Chem.*, vol.  
422 62, p. 91- 123, 2019.
- 423 [8] S. M. Moghimi, A. C. Hunter, et J. C. Murray, « Nanomedicine : current status and future  
424 prospects », *FASEB J.*, vol. 19, p. 311- 330, 2005.
- 425 [9] F. Farjadian, A. Ghasemi, O. Gohari, A. Roointan, et M. Karimi, « Nanopharmaceuticals and  
426 nanomedicines currently on the market : challenges and opportunities », *Nanomed.*, vol. 14, p.  
427 93- 126, 2019.
- 428 [10] D. Lombardo, M. A. Kiselev, et M. T. Caccamo, « Smart Nanoparticles for Drug Delivery  
429 Application : Development of Versatile Nanocarrier Platforms in Biotechnology and  
430 Nanomedicine », *J. Nanomater.*, vol. 2019, p. 1- 26, 2019.
- 431 [11] A. Khdaïr *et al.*, « Modified-chitosan nanoparticles: Novel drug delivery systems improve oral  
432 bioavailability of doxorubicin », *Eur. J. Pharm. Sci.*, vol. 93, p. 38- 44, 2016.
- 433 [12] S. Doppalapudi, A. Jain, D. K. Chopra, et W. Khan, « Psoralen loaded liposomal nanocarriers for  
434 improved skin penetration and efficacy of topical PUVA in psoriasis », *Eur. J. Pharm. Sci.*, vol. 96,  
435 p. 515- 529, 2017.
- 436 [13] O. S. Qureshi *et al.*, « Sustained release docetaxel-incorporated lipid nanoparticles with  
437 improved pharmacokinetics for oral and parenteral administration », *J. Microencapsul.*, vol. 34,  
438 n° 3, p. 250- 261, 2017.
- 439 [14] K. M. El-say et H. S. El-sawy, « Polymeric nanoparticles : Promising platform for drug delivery »,  
440 *Int. J. Pharm.*, vol. 528, n° 1- 2, p. 675- 691, 2017.
- 441 [15] S. Rani, A. K. Sharma, I. Khan, et A. Gothwal, *Polymeric Nanoparticles in Targeting and Delivery of*  
442 *Drugs*. Elsevier Inc., 2017.
- 443 [16] T. M. Allen et P. R. Cullis, « Liposomal drug delivery systems: from concept to clinical  
444 applications », *Adv. Drug Deliv. Rev.*, vol. 65, n° 1, p. 36–48, 2013.

- 445 [17] M. L. Immordino, F. Dosio, et L. Cattel, « Stealth liposomes: review of the basic science, rationale,  
446 and clinical applications, existing and potential », *Int. J. Nanomedicine*, vol. 1, n° 3, p. 297- 315,  
447 2006.
- 448 [18] W. Mehnert et K. Mäder, « Solid lipid nanoparticles: Production, characterization and  
449 applications », *Adv. Drug Deliv. Rev.*, vol. 64, p. 83- 101, 2012.
- 450 [19] M. Geszke-Moritz et M. Moritz, « Solid lipid nanoparticles as attractive drug vehicles:  
451 Composition, properties and therapeutic strategies », *Mater. Sci. Eng. C*, vol. 68, p. 982- 944,  
452 2016.
- 453 [20] C. I. C. Crucho et M. T. Barros, « Polymeric nanoparticles: A study on the preparation variables  
454 and characterization methods », *Mater. Sci. Eng. C*, vol. 80, p. 771- 784, 2017.
- 455 [21] S. Mallakpour et V. Behranvand, « Polymeric nanoparticles : Recent development in synthesis  
456 and application », *Express Polym. Lett.*, vol. 10, n° 11, p. 895- 913, 2016.
- 457 [22] L. A. Frank, R. V Contri, R. C. R. Beck, A. R. Pohlmann, et S. S. Guterres, « Improving drug  
458 biological effects by encapsulation into polymeric nanocapsules », *Adv. Rev.*, vol. 7, p. 623- 639,  
459 2015.
- 460 [23] S. Amoabediny, G Haghirsadat, F Naderinezhad, M. N. Helder, J. Akhoundi Kharanaghi, E  
461 Mohammadnejad Arough, et B. Zandieh-Doulabi, « Overview of preparation methods of  
462 polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles: A comprehensive  
463 review », *Int. J. Polym. Mater. Polym. Biomater.*, vol. 67, n° 6, p. 383–400, 2017.
- 464 [24] S. P. Egusquiaguirre, J. L. Pedraz, R. M. Hernández, et M. Igartua, « 29 - Nanotherapeutic  
465 Platforms for Cancer Treatment: From Preclinical Development to Clinical Application », in  
466 *Nanoarchitectonics for Smart Delivery and Drug Targeting*, 2016, p. 813- 869.
- 467 [25] P. M. Campos, M. V. L. BadraBentley, et V. P. Torchilin, « Chapter 1 - Nanopreparations for skin  
468 cancer therapy », in *Nanobiomaterials in Cancer Therapy: Applications of Nanobiomaterials  
469 Volume 7*, 2016, p. 1- 28.
- 470 [26] E. Calzoni, A. Cesaretti, A. Polchi, A. Di Michele, B. Tancini, et C. Emiliani, « Biocompatible  
471 Polymer Nanoparticles for Drug Delivery Applications in Cancer and Neurodegenerative Disorder  
472 Therapies », *J. Funct. Biomater.*, vol. 10, n° 4, p. 1- 15, 2019.
- 473 [27] H. Zazo, C. I. Colino, et J. M. Lanao, « Current applications of nanoparticles in infectious  
474 diseases », *J. Controlled Release*, vol. 224, p. 86- 102, 2016.
- 475 [28] J. P. Rao et K. E. Geckeler, « Polymer nanoparticles : Preparation techniques and size-control  
476 parameters », *Prog. Polym. Sci.*, vol. 36, n° 7, p. 887- 913, 2011.
- 477 [29] K. Krishnaswamy et V. Orsat, « Chapter 2 - Sustainable Delivery Systems Through Green  
478 Nanotechnology », in *Nano- and Microscale Drug Delivery Systems Design and Fabrication*, 2017,  
479 p. 17- 32.
- 480 [30] H. Fessi, F. Puisieux, J. Ph. Devissaguet, N. Ammoury, et S. Benita, « Nanocapsule formation by  
481 interfacial polymer deposition following solvent displacement », *Int. J. Pharm.*, vol. 55, n° 1, p.  
482 R1- R4, 1989.
- 483 [31] F. Haghirsadat, G. Amoabediny, et S. Naderinezhad, « Overview of Preparation Methods of  
484 Polymeric and Lipid-Based ( Niosome , Solid Lipid , Liposome ) Nanoparticles : A Comprehensive  
485 Review », *Int. J. Polym. Mater. Polym. Biomater.*, p. 1- 74, 2017.
- 486 [32] P. Couvreur, G. Barratt, E. Fattal, P. Legrand, et C. Vauthier, « Nanocapsule technology: a  
487 review », *Crit. Rev. Ther. Drug Carr. Syst.*, vol. 19, p. 99- 134, 2002.
- 488 [33] « Nanoprecipitation of cellulose acetate using solvent/nonsolvent mixtures as dispersive media -  
489 ScienceDirect ». [En ligne]. Disponible sur:  
490 <https://www.sciencedirect.com/science/article/pii/S0927775710006606?via%3Dihub>. [Consulté  
491 le: 13-juill-2019].
- 492 [34] A. Albisa, E. Piacentini, V. Sebastian, M. Arruebo, J. Santamaria, et L. Giorno, « Preparation of  
493 Drug-Loaded PLGA-PEG Nanoparticles by Membrane-Assisted Nanoprecipitation », *Pharm. Res.*,  
494 vol. 34, n° 6, p. 1296- 1308, juin 2017.

- 495 [35] A. Maaz, W. Abdelwahed, I. A. Tekko, et S. Trefi, « Influence of nanoprecipitation method  
496 parameters on nanoparticles loaded with gatifloxacin for ocular drug delivery », *Int. J. Acad. Sci.*  
497 *Res.*, vol. 3, n° 1, p. 1- 12, 2015.
- 498 [36] S. Arpicco, L. Battaglia, P. Brusa, R. Cavalli, D. Chirio, et F. Dosio, « Recent studies on the delivery  
499 of hydrophilic drugs in nanoparticulate systems », *J. Drug Deliv. Sci. Technol.*, vol. 32, p.  
500 298- 312, 2016.
- 501 [37] J. W. Vanderhoff et M. S. El Asser, « Polymer emulsification process », 1979.
- 502 [38] C. Vauthier et K. Bouchemal, « Methods for the preparation and manufacture of polymeric  
503 nanoparticles », *Pharm. Res.*, vol. 5, p. 1025–1058., 2009.
- 504 [39] N. Garti et C. Bisperink, « Double emulsions: Progress and applications », *Curr. Opin. Colloid*  
505 *Interface Sci.*, vol. 3, n° 6, p. 657–667, 1998.
- 506 [40] M. Iqbal, J. P. Valour, H. Fessi, et A. Elaissari, « Preparation of biodegradable PCL particles via  
507 double emulsion evaporation method using ultrasound technique », *Colloid Polym. Sci.*, vol. 293,  
508 n° 3, p. 861–873, 2015.
- 509 [41] P. Calvo, J. L. Remunan Lopez, Vila-Jato, et M. J. Alonso, « Novel Hydrophilic Chitosan –  
510 Polyethylene Oxide Nanoparticles as Protein Carriers », *J. Appl. Polym. Sci.*, vol. 63, p. 125- 132,  
511 1997.
- 512 [42] J. Yang, S. Han, H. Zheng, H. Dong, et J. Liu, « Preparation and application of micro/nanoparticles  
513 based on natural polysaccharides », *Carbohydr. Polym.*, vol. 123, p. 53- 66, 2015.
- 514 [43] V. J. Mohanraj et Y. Chen, « Nanoparticles – A Review », *Trop. J. Pharm. Res.*, vol. 5, n° 1, p.  
515 561- 573, 2006.
- 516 [44] B. V. N. Nagavarma, H. K. S. Yadav, A. Ayaz, L. S. Vasudha, et H. G. Shivakumar, « Different  
517 techniques for preparation of polymeric nanoparticles-A review. », *Asian J. Pharm. Clin. Res.*, vol.  
518 5, n° 3, 2012.
- 519 [45] T. López-León, E. L. S. Carvalho, B. Seijo, J. L. Ortega-Vinuesa, et D. Bastos-González,  
520 « Physicochemical characterization of chitosan nanoparticles: electrokinetic and stability  
521 behavior », *J. Colloid Interface Sci.*, vol. 283, p. 344- 51, 2005.
- 522 [46] S. Kunjachan, S. Jose, et T. Lammers, « Understanding the mechanism of ionic gelation for  
523 synthesis of chitosan nanoparticles using qualitative techniques », *Asian J. Pharm.*, p. 148- 153,  
524 2010.
- 525 [47] S. Usmiati, N. Richana, D. Mangunwidjaja, E. Noor, et E. Prangdimurti, « The Using of Ionic  
526 Gelation Method Based on Polysaccharides for Encapsulating the Macromolecules– A Review »,  
527 *Int. Conf. Food Secur. Nutr.*, vol. 67, 2014.
- 528 [48] A. T. Miah, S. K. Bharadwaj, et P. Saikia, « Surfactant free synthesis of gold nanoparticles within  
529 meso-channels of non-functionalized SBA-15 for its promising catalytic activity », *Powder*  
530 *Technol.*, vol. 315, p. 147- 156, juin 2017.
- 531 [49] K. S. Soppimath, T. M. Aminabhavi, A. R. Kulkarni, et W. E. Rudzinski, « Biodegradable polymeric  
532 nanoparticles as drug delivery devices », *J. Controlled Release*, vol. 70, p. 1- 20, 2001.
- 533 [50] K. Ranjit et A. A. Baquee, « Nanoparticle: An overview of preparation, characterization and  
534 application », *Int. Res. J. Pharm.*, vol. 4, n° 4, p. 47- 57, 2013.
- 535 [51] A. D. Bangham, M. M. Standish, et J. C. Watkins, « Diffusion of univalent ions across the lamellae  
536 of swollen phospholipids », *J. Mol. Biol.*, vol. 13, n° 1, p. 238-277, août 1965.
- 537 [52] M. Li *et al.*, « Composition design and medical application of liposomes », *Eur. J. Med. Chem.*, vol.  
538 164, p. 640- 653, févr. 2019.
- 539 [53] V. Van Tran, J.-Y. Moon, et Y.-C. Lee, « Liposomes for delivery of antioxidants in cosmeceuticals:  
540 Challenges and development strategies », *J. Controlled Release*, vol. 300, p. 114- 140, avr. 2019.
- 541 [54] « Drug carriers in osteoporosis: Preparation, drug encapsulation and applications -  
542 ScienceDirect ». [En ligne]. Disponible sur:  
543 <https://www.sciencedirect.com/science/article/pii/S0378517313000628>. [Consulté le: 18-mai-  
544 2019].
- 545 [55] Y. P. Patil et S. Jadhav, « Novel methods for liposome preparation », *Chem. Phys. Lipids*, vol. 177,  
546 p. 8- 18, janv. 2014.

- 547 [56] A. Akbarzadeh *et al.*, « Liposome: classification, preparation, and applications », *Nanoscale Res.*  
548 *Lett.*, vol. 8, n° 1, p. 102, févr. 2013.
- 549 [57] R. Gharib, H. Greige-Gerges, S. Fourmentin, et C. Charcosset, « Hydroxypropyl- $\beta$ -cyclodextrin as a  
550 membrane protectant during freeze-drying of hydrogenated and non-hydrogenated liposomes  
551 and molecule-in-cyclodextrin-in- liposomes: Application to trans-anethole », *Food Chem.*, vol.  
552 267, p. 67- 74, nov. 2018.
- 553 [58] S. Batzri et E. D. Korn, « Single bilayer liposomes prepared without sonication », *Biochim.*  
554 *Biophys. Acta BBA - Biomembr.*, vol. 298, n° 4, p. 1015- 1019, avr. 1973.
- 555 [59] A. Laouini, C. Jaafar-Maalej, I. Limayem-Blouza, S. Sfar, C. Charcosset, et H. Fessi, « Preparation,  
556 Characterization and Applications of Liposomes: State of the Art », déc-2012. [En ligne].  
557 Disponible sur:  
558 <https://www.ingentaconnect.com/content/asp/jcsb/2012/00000001/00000002/art00001;jsessionid=1kfu9jix11x10.x-ic-live-01>. [Consulté le: 05-juin-2019].
- 560 [60] S. Kaddah, N. Khreich, F. Kaddah, C. Charcosset, et H. Greige-Gerges, « Cholesterol modulates  
561 the liposome membrane fluidity and permeability for a hydrophilic molecule », *Food Chem.*  
562 *Toxicol.*, vol. 113, p. 40- 48, mars 2018.
- 563 [61] Z. Huang *et al.*, « Progress involving new techniques for liposome preparation », *Asian J. Pharm.*  
564 *Sci.*, vol. 9, n° 4, p. 176- 182, août 2014.
- 565 [62] C. Jaafar-Maalej, C. Charcosset, et H. Fessi, « A new method for liposome preparation using a  
566 membrane contactor », *J. Liposome Res.*, vol. 21, n° 3, p. 213- 220, sept. 2011.
- 567 [63] A. Laouini, C. Jaafar-Maalej, S. Sfar, C. Charcosset, et H. Fessi, « Liposome preparation using a  
568 hollow fiber membrane contactor--application to spironolactone encapsulation », *Int. J. Pharm.*,  
569 vol. 415, n° 1- 2, p. 53- 61, août 2011.
- 570 [64] T. T. Pham, C. Jaafar-Maalej, C. Charcosset, et H. Fessi, « Liposome and niosome preparation  
571 using a membrane contactor for scale-up », *Colloids Surf. B Biointerfaces*, vol. 94, p. 15- 21, juin  
572 2012.
- 573 [65] C. Jaafar-Maalej, A. Elaissari, et H. Fessi, « Lipid-based carriers: manufacturing and applications  
574 for pulmonary route », *Expert Opin. Drug Deliv.*, vol. 9, n° 9, p. 1111- 1127, sept. 2012.
- 575 [66] L. Bayón-Cordero, I. Alkorta, et L. Arana, « Application of Solid Lipid Nanoparticles to Improve the  
576 Efficiency of Anticancer Drugs », *Nanomaterials*, vol. 9, n° 3, p. 474, mars 2019.
- 577 [67] « Solid lipid nanocarriers in drug delivery: characterization and design: Expert Opinion on Drug  
578 Delivery: Vol 15, No 8 ». [En ligne]. Disponible sur:  
579 <https://www.tandfonline.com/doi/full/10.1080/17425247.2018.1504018>. [Consulté le: 13-juill-  
580 2019].
- 581 [68] M. Geszke-Moritz et M. Moritz, « Solid lipid nanoparticles as attractive drug vehicles:  
582 Composition, properties and therapeutic strategies », *Mater. Sci. Eng. C*, vol. 68, p. 982- 994,  
583 nov. 2016.
- 584 [69] C. Dumont, S. Bourgeois, H. Fessi, et V. Jannin, « Lipid-based nanosuspensions for oral delivery of  
585 peptides, a critical review », *Int. J. Pharm.*, vol. 541, n° 1- 2, p. 117- 135, avr. 2018.
- 586 [70] R. H. Müller, K. Mäder, et S. Gohla, « Solid lipid nanoparticles (SLN) for controlled drug delivery -  
587 a review of the state of the art », *Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Pharm.*  
588 *Verfahrenstechnik EV*, vol. 50, n° 1, p. 161- 177, juill. 2000.
- 589 [71] M. Trotta, F. Debernardi, et O. Caputo, « Preparation of solid lipid nanoparticles by a solvent  
590 emulsification-diffusion technique », *Int. J. Pharm.*, vol. 257, n° 1- 2, p. 153- 160, mai 2003.
- 591 [72] Gasco, Maria R., « Method for producing solid lipid microspheres having a narrow size  
592 distribution », US 5,250,236 A.
- 593 [73] S. Das et A. Chaudhury, « Recent Advances in Lipid Nanoparticle Formulations with Solid Matrix  
594 for Oral Drug Delivery », *AAPS PharmSciTech*, vol. 12, n° 1, p. 62- 76, mars 2011.
- 595 [74] K. Miladi, D. Ibraheem, M. Iqbal, S. Sfar, H. Fessi, et A. Elaissari, « Particles from preformed  
596 polymers as carriers for drug delivery », *EXCLI J.*, vol. 13, p. 28- 57, 2014.

- 597 [75] M. García-Fuentes, D. Torres, et M. J. Alonso, « Design of lipid nanoparticles for the oral delivery  
598 of hydrophilic macromolecules », *Colloids Surf. B Biointerfaces*, vol. 27, n° 2- 3, p. 159- 168, févr.  
599 2003.
- 600 [76] R. Duncan, « Polymer therapeutics: Top 10 selling pharmaceuticals - what next? », *J. Control.*  
601 *Release Off. J. Control. Release Soc.*, vol. 190, p. 371- 380, sept. 2014.
- 602 [77] D. Bobo, K. J. Robinson, J. Islam, K. J. Thurecht, et S. R. Corrie, « Nanoparticle-Based Medicines: A  
603 Review of FDA-Approved Materials and Clinical Trials to Date », *Pharm. Res.*, vol. 33, n° 10, p.  
604 2373- 2387, 2016.
- 605 [78] P. Skupin-Mrugalska, « Chapter 6 - Liposome-Based Drug Delivery for Lung Cancer », in  
606 *Nanotechnology-Based Targeted Drug Delivery Systems for Lung Cancer*, P. Kesharwani, Éd.  
607 Academic Press, 2019, p. 123- 160.
- 608 [79] G. Poovi et N. Damodharan, « Lipid nanoparticles: A challenging approach for oral delivery of BCS  
609 Class-II drugs », *Future J. Pharm. Sci.*, vol. 4, n° 2, p. 191- 205, déc. 2018.
- 610 [80] A. M. Nasef, A. R. Gardouh, et M. M. Ghorab, « Formulation and in-vitro evaluation of  
611 pantoprazole loaded pH-sensitive polymeric nanoparticles », *Future J. Pharm. Sci.*, vol. 3, n° 2, p.  
612 103- 117, déc. 2017.
- 613 [81] A. A. Alhowyan *et al.*, « Antifungal efficacy of Itraconazole loaded PLGA-nanoparticles stabilized  
614 by vitamin-E TPGS: In vitro and ex vivo studies », *J. Microbiol. Methods*, vol. 161, p. 87- 95, juin  
615 2019.
- 616 [82] R. Domínguez-Ríos *et al.*, « Cisplatin-loaded PLGA nanoparticles for HER2 targeted ovarian cancer  
617 therapy », *Colloids Surf. B Biointerfaces*, vol. 178, p. 199- 207, juin 2019.
- 618 [83] R. Barbara *et al.*, « Novel Curcumin loaded nanoparticles engineered for Blood-Brain Barrier  
619 crossing and able to disrupt Abeta aggregates », *Int. J. Pharm.*, vol. 526, n° 1, p. 413- 424, juin  
620 2017.
- 621 [84] C. Monterrubio *et al.*, « Targeted drug distribution in tumor extracellular fluid of GD2-expressing  
622 neuroblastoma patient-derived xenografts using SN-38-loaded nanoparticles conjugated to the  
623 monoclonal antibody 3F8 », *J. Controlled Release*, vol. 255, p. 108- 119, juin 2017.
- 624 [85] A. Saneja *et al.*, « Gemcitabine and betulinic acid co-encapsulated PLGA-PEG polymer  
625 nanoparticles for improved efficacy of cancer chemotherapy », *Mater. Sci. Eng. C*, vol. 98, p.  
626 764- 771, mai 2019.
- 627 [86] S. Pieper et K. Langer, « Doxorubicin-loaded PLGA nanoparticles - a systematic evaluation of  
628 preparation techniques and parameters\* », *Mater. Today Proc.*, vol. 4, p. S188- S192, janv. 2017.
- 629 [87] D. Deepika, H. K. Dewangan, L. Maurya, et S. Singh, « Intranasal Drug Delivery of Frovatriptan  
630 Succinate-Loaded Polymeric Nanoparticles for Brain Targeting », *J. Pharm. Sci.*, vol. 108, n° 2, p.  
631 851- 859, févr. 2019.
- 632 [88] Y. A. Skorik *et al.*, « Development of drug delivery systems for taxanes using ionic gelation of  
633 carboxyacyl derivatives of chitosan », *Carbohydr. Polym.*, vol. 162, p. 49- 55, avr. 2017.
- 634 [89] T. Gomathi, P. N. Sudha, J. A. K. Florence, J. Venkatesan, et S. Anil, « Fabrication of letrozole  
635 formulation using chitosan nanoparticles through ionic gelation method », *Int. J. Biol. Macromol.*,  
636 vol. 104, p. 1820- 1832, nov. 2017.
- 637 [90] « Enhancement of oral bioavailability of poorly water soluble carvedilol by chitosan  
638 nanoparticles: Optimization and pharmacokinetic study - ScienceDirect ». [En ligne]. Disponible  
639 sur: <https://www.sciencedirect.com/science/article/pii/S0141813019318999>. [Consulté le: 06-  
640 juin-2019].
- 641 [91] H.-H. Peng, D.-X. Hong, Y.-X. Guan, et S.-J. Yao, « Preparation of pH-responsive DOX-loaded  
642 chitosan nanoparticles using supercritical assisted atomization with an enhanced mixer », *Int. J.*  
643 *Pharm.*, vol. 558, p. 82- 90, mars 2019.
- 644 [92] A. Alomrani *et al.*, « The use of chitosan-coated flexible liposomes as a remarkable carrier to  
645 enhance the antitumor efficacy of 5-fluorouracil against colorectal cancer », *Saudi Pharm. J.*,  
646 mars 2019.

- 647 [93] V. Dave, A. Gupta, P. Singh, C. Gupta, V. Sadhu, et K. R. Reddy, « Synthesis and characterization  
648 of celecoxib loaded PEGylated liposome nanoparticles for biomedical applications », *Nano-  
649 Struct. Nano-Objects*, vol. 18, p. 100288, avr. 2019.
- 650 [94] Q. Jin *et al.*, « TPGS modified nanoliposomes as an effective ocular delivery system to treat  
651 glaucoma », *Int. J. Pharm.*, vol. 553, n° 1- 2, p. 21- 28, déc. 2018.
- 652 [95] D. K. Karumanchi, Y. Skrypai, A. Thomas, et E. R. Gaillard, « Rational design of liposomes for  
653 sustained release drug delivery of bevacizumab to treat ocular angiogenesis », *J. Drug Deliv. Sci.  
654 Technol.*, vol. 47, p. 275- 282, oct. 2018.
- 655 [96] S. Handali *et al.*, « A novel 5-Fluorouracil targeted delivery to colon cancer using folic acid  
656 conjugated liposomes », *Biomed. Pharmacother. Biomedecine Pharmacother.*, vol. 108, p.  
657 1259- 1273, déc. 2018.
- 658 [97] G. Tan *et al.*, « Bioadhesive chitosan-loaded liposomes: A more efficient and higher permeable  
659 ocular delivery platform for timolol maleate », *Int. J. Biol. Macromol.*, vol. 94, n° Pt A, p.  
660 355- 363, janv. 2017.
- 661 [98] T. Wang, Y. Jiang, H. Chu, X. Liu, Y. Dai, et D. Wang, « Doxorubicin and Lovastatin co-delivery  
662 liposomes for synergistic therapy of liver cancer », *J. Drug Deliv. Sci. Technol.*, vol. 52, p.  
663 452- 459, août 2019.
- 664 [99] G. K. Zorzi, R. S. Schuh, V. J. Maschio, N. T. Brazil, M. B. Rott, et H. F. Teixeira, « Box Behnken  
665 design of siRNA-loaded liposomes for the treatment of a murine model of ocular keratitis caused  
666 by *Acanthamoeba* », *Colloids Surf. B Biointerfaces*, vol. 173, p. 725- 732, janv. 2019.
- 667 [100] K. Sen, S. Banerjee, et M. Mandal, « Dual drug loaded liposome bearing apigenin and 5-  
668 Fluorouracil for synergistic therapeutic efficacy in colorectal cancer », *Colloids Surf. B  
669 Biointerfaces*, vol. 180, p. 9- 22, août 2019.
- 670 [101] W. Yang, Q. Hu, Y. Xu, H. Liu, et L. Zhong, « Antibody fragment-conjugated gemcitabine and  
671 paclitaxel-based liposome for effective therapeutic efficacy in pancreatic cancer », *Mater. Sci.  
672 Eng. C*, vol. 89, p. 328- 335, août 2018.
- 673 [102] F. ud Din, A. Zeb, K. U. Shah, et Zia-ur-Rehman, « Development, in-vitro and in-vivo  
674 evaluation of ezetimibe-loaded solid lipid nanoparticles and their comparison with marketed  
675 product », *J. Drug Deliv. Sci. Technol.*, vol. 51, p. 583- 590, juin 2019.
- 676 [103] A. C. Silva *et al.*, « Preparation, characterization and biocompatibility studies on risperidone-  
677 loaded solid lipid nanoparticles (SLN): High pressure homogenization versus ultrasound »,  
678 *Colloids Surf. B Biointerfaces*, vol. 86, n° 1, p. 158- 165, août 2011.

679

680