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Encapsulation methods of active molecules for drug delivery

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OUTLINE

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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.

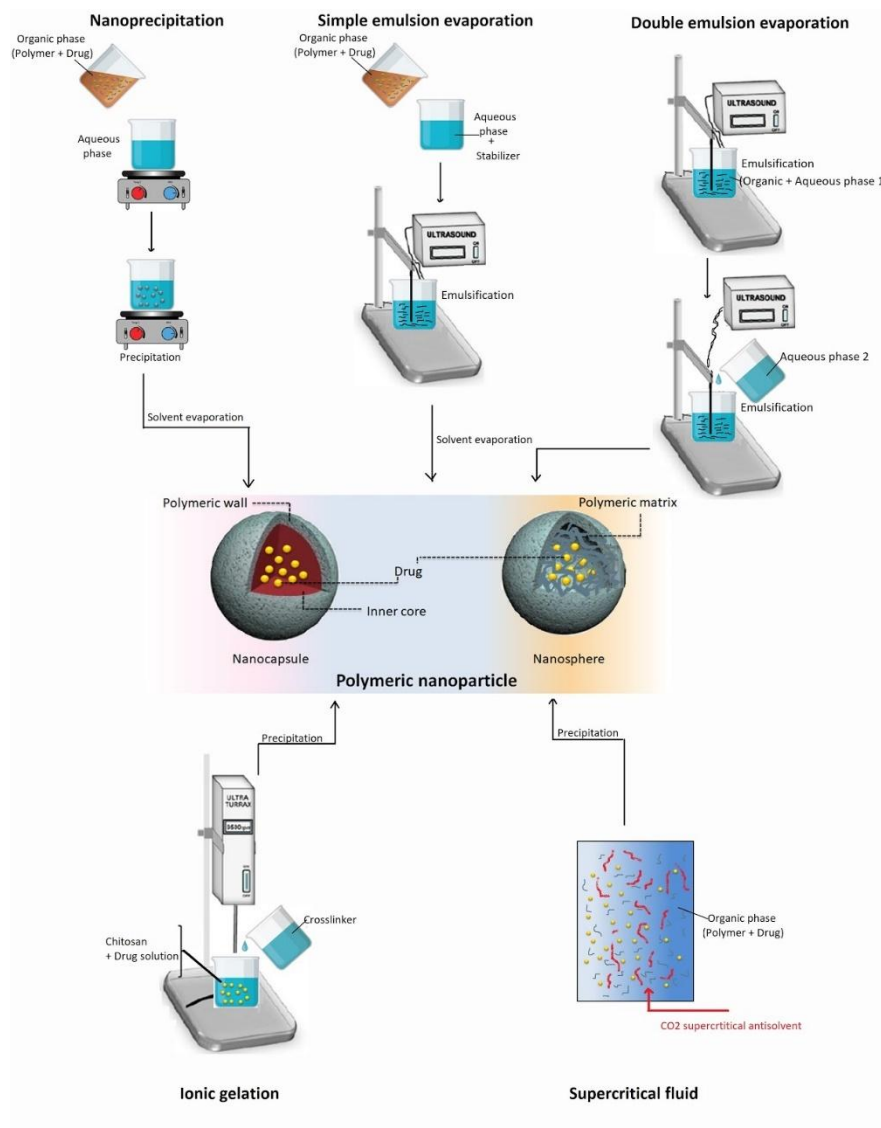
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95 **2. Polymer-based nanoparticles**

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.

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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
171 **2.4. Ionic gelation**

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

184
185 **2.5. Supercritical fluid method**

186 All the above methods often involve the use of toxic solvents and / or surfactants that
187 are dangerous to the environment as well as to physiological systems [48]. Consequently,
188 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 CO₂ 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].

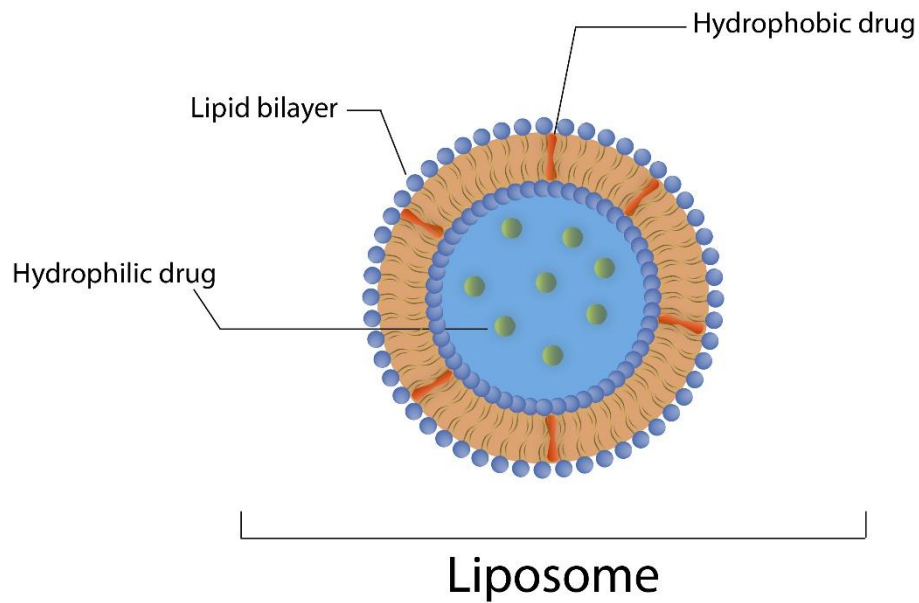
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200 **3. Liposomes**

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.

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

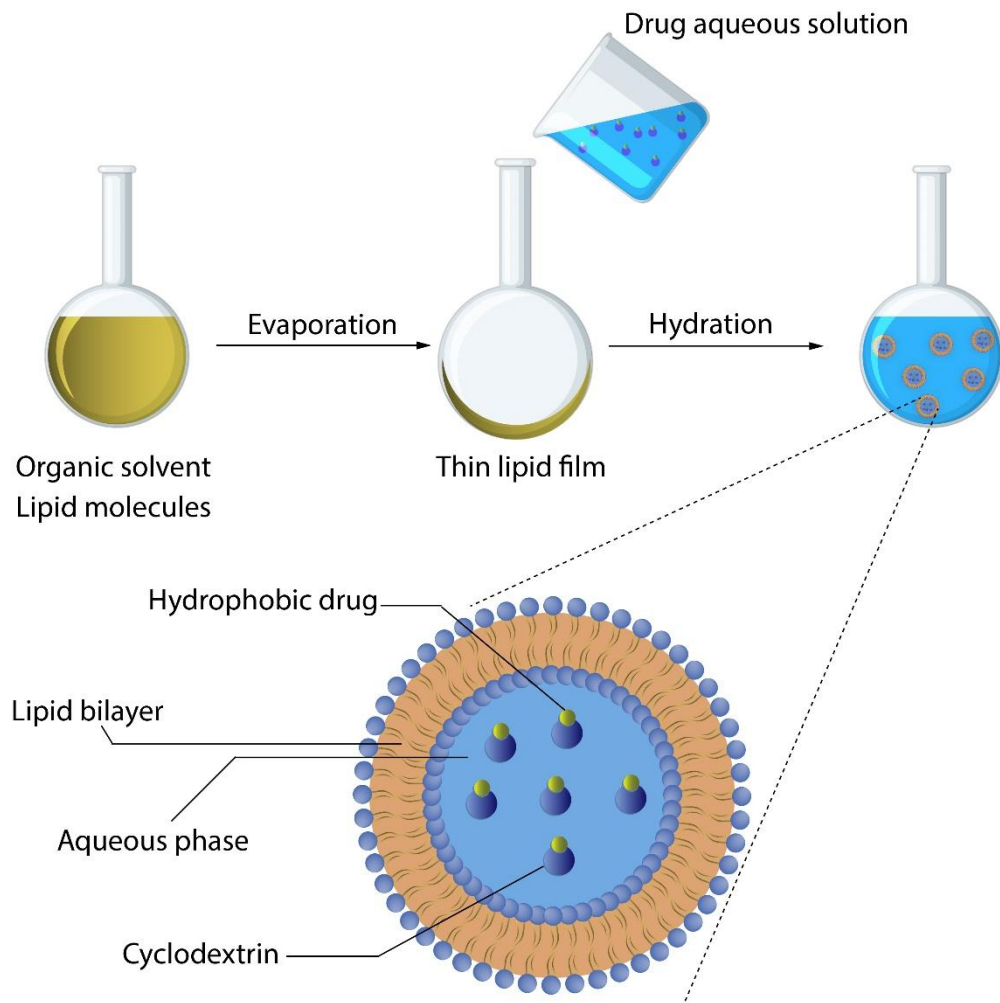
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216 **3.1.Hydration of a Thin Lipid Film**

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).**

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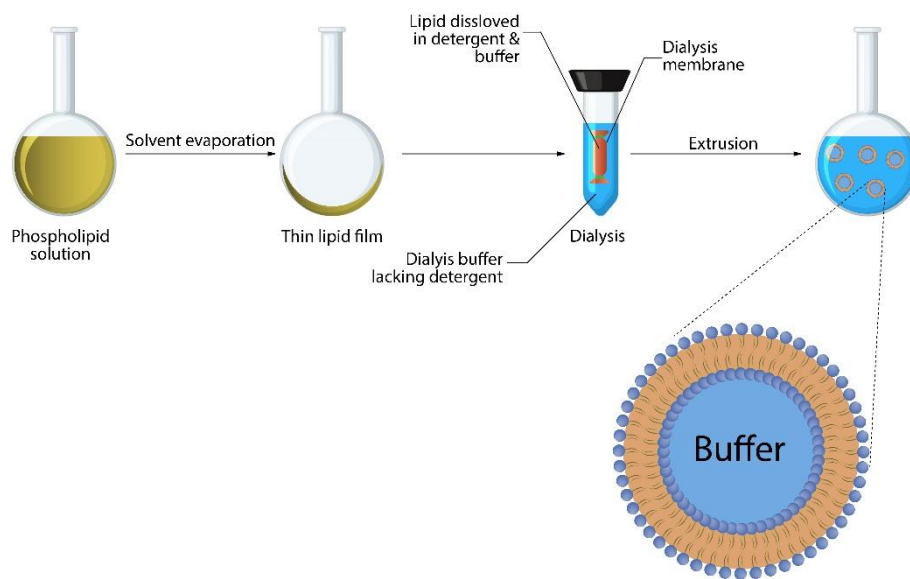
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231 **3.2.Detergent Dialysis**

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



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Figure 4. Detergent dialysis method.

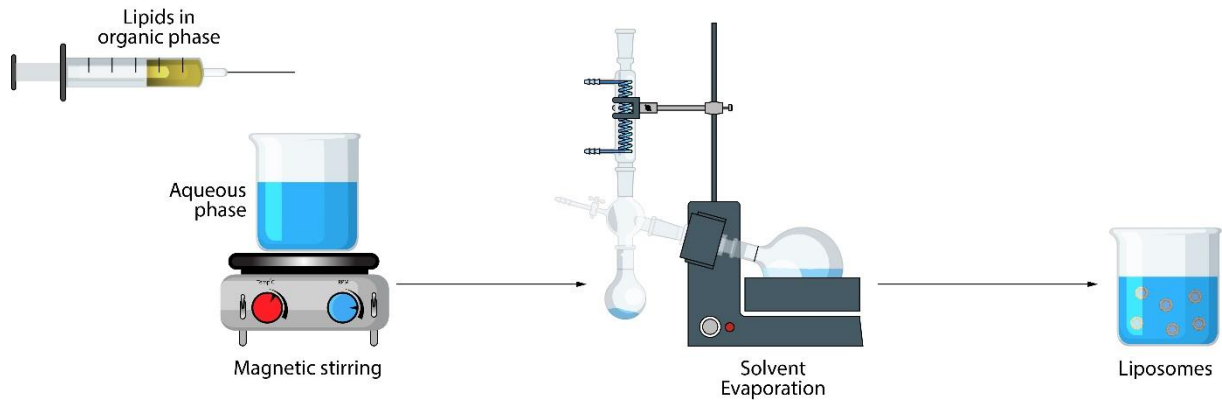
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245 3.3.Solvent Injection Technique

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].



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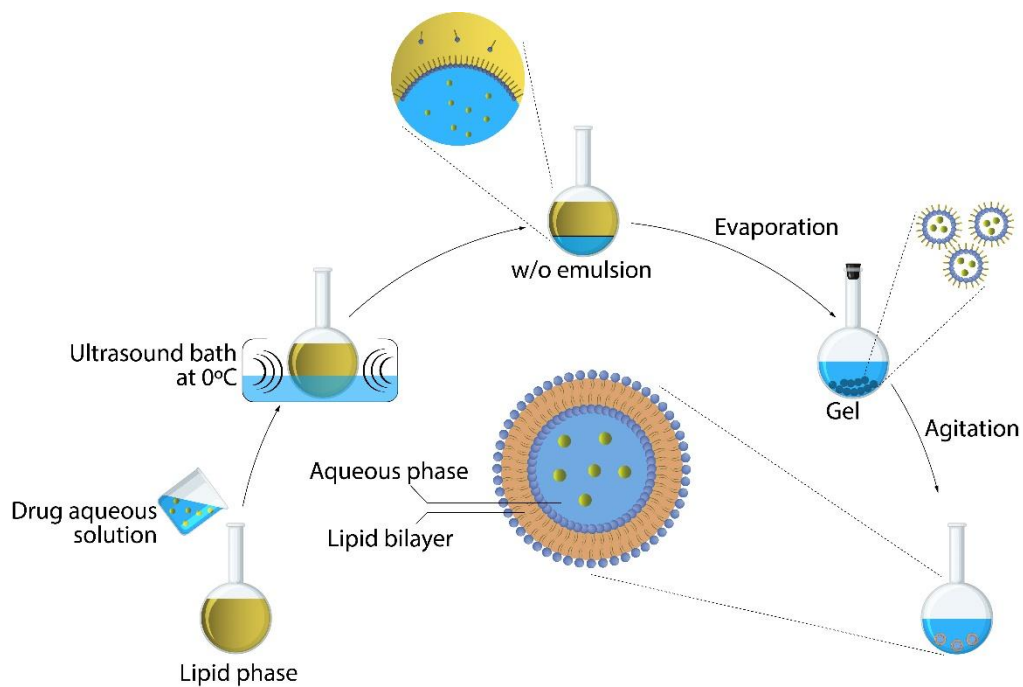
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Figure 5. Solvent injection technique.

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].



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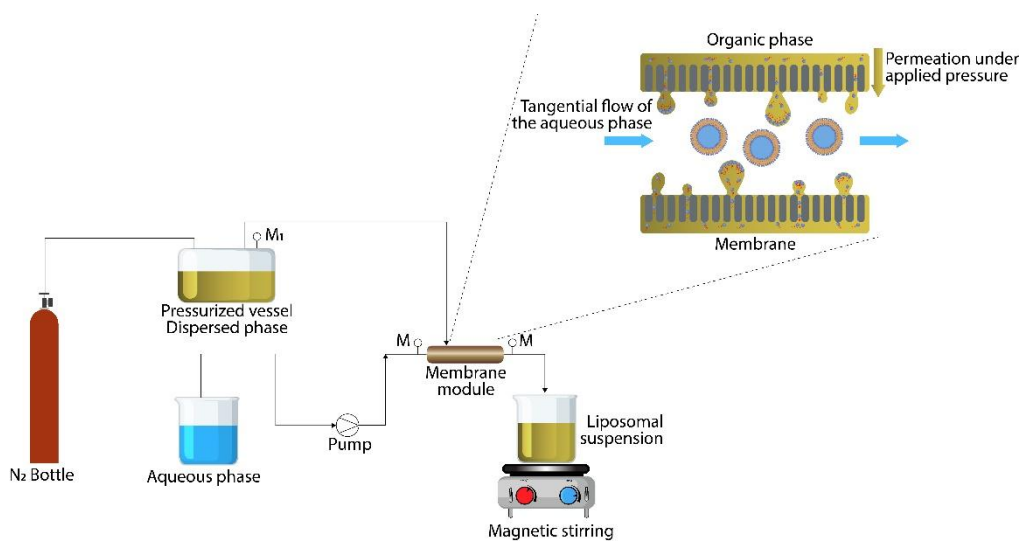
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Figure 6. Reverse phase evaporation technique

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.

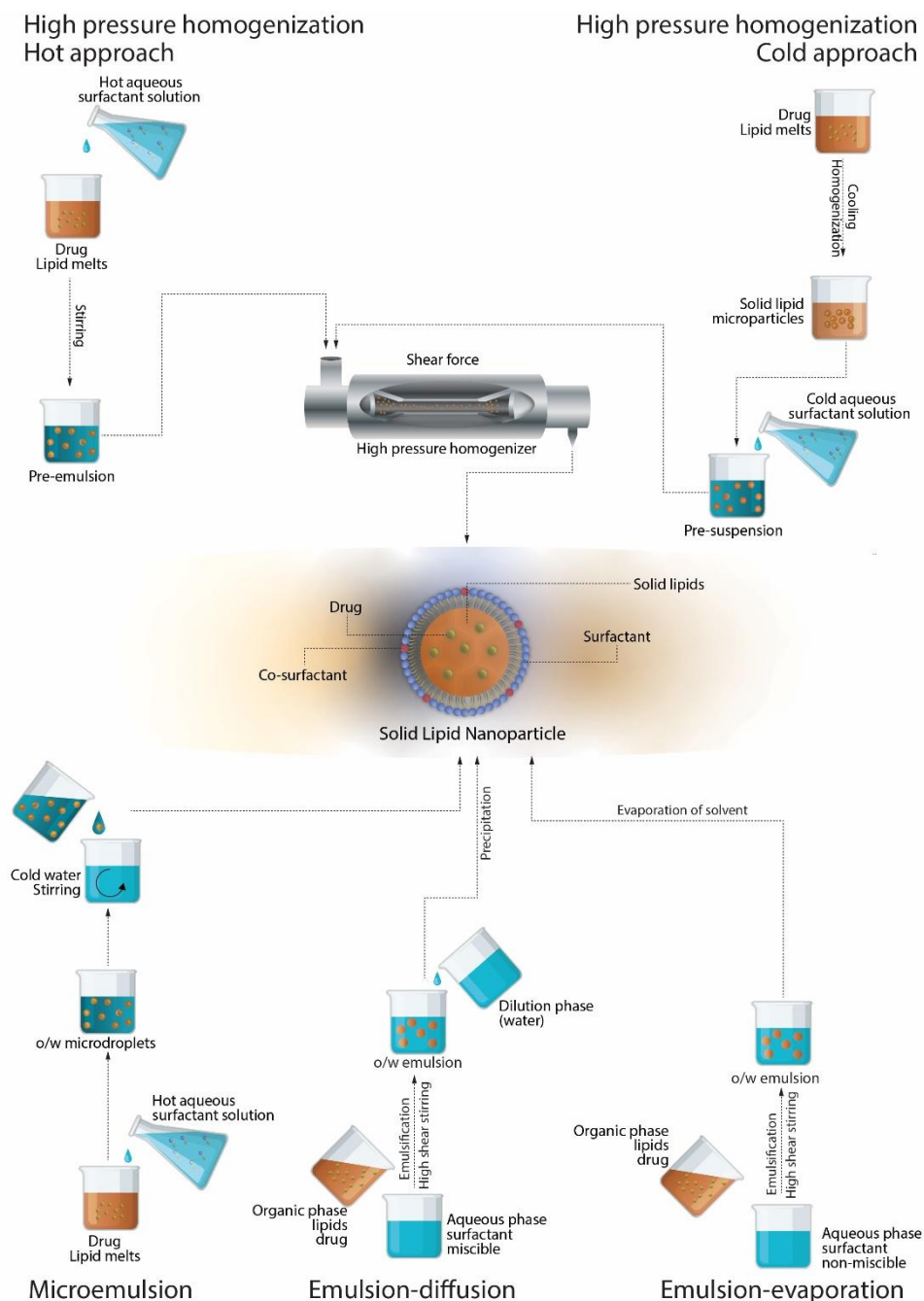
333 Different types of surfactants and co-surfactants were used in this method such as lecithin,
334 biliary salts, and alcohols. In addition, it is important that during the precipitation step, mixing
335 should be done by mild mechanical agitation to guarantee that the small size of the obtained
336 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 ₂ (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]
<i>Liposomes</i>						
Thin film hydration	Phosphatidylcholine, cholesterol, Dicytlylphosphate	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]
<i>Solid lipid nanoparticles</i>						
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 **Conclusion**

381

382 Nanomedicine offers an enormous outlook for upgrading current therapies and

383 emerging new treatment tools for illness previously assumed difficult or impossible to treat.

384 Nanostructured systems have shown exciting benefits due to their size and shape since they

385 can reach areas which are inaccessible using other conventional drug delivery systems protect

386 the drug molecules from premature degradation, sudden clearance, and toxic manifestations.

387 Nanostructured systems can also deliver the drug to a specific tissue site or cell leading to

388 increased drug amounts at a local site hence enhancing the therapeutic profile. In this chapter,

389 we spotlight recent advances of both lipid and polymer based-nanocarriers such as liposomes,

390 solid lipid nanoparticles and polymeric nanoparticles in the emergence of new concepts for

391 the efficient transport of drug molecules. The first section of this review has provided

392 information about the properties and recent developments in the synthesis of these

393 nanosystems. Several methods have been explored for nanocarrier preparation, nonetheless,

394 the choice of the appropriate approach is a crucial key to gain specific requirements.

395 Additionally, this paper has reviewed current applications of these carriers. The discussed

396 nanostructured systems provide interesting perspectives for applications in several fields such

397 as drug and gene delivery, biomedical imaging, diagnosis, and theranostics. The specific

398 functionalization of the carrier surface can enhance its biodistribution to target cells and limit

399 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.

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404 **References:**

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