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# Pickering nano-emulsions stabilized by Eudragit RL100 nanoparticles as oral drug delivery system for poorly soluble drugs

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34 **ABSTRACT**

35 The purpose of this study was to develop Pickering water-in-oil nano-emulsions only  
36 stabilized by Eudragit RL100 nanoparticles (NPs), in order to increase the nano-emulsion  
37 stability and create a barrier to improve the drug encapsulation and better control the drug  
38 release. The first part of this study was dedicated to investigating the nano-emulsion  
39 formulation by ultrasonication and understanding the interfacial behavior and role of NPs in  
40 the stabilization of the water/oil interface. The focus was on the surface coverage in the  
41 function of the formulation parameters (volume fractions) to disclose the extents and  
42 limitations of the process. The main physicochemical analysis of the Pickering nano-  
43 emulsions was performed by dynamic light scattering and transmission electron microscopy.  
44 On the other hand, the second experimental approach was dedicated to understanding the  
45 interfacial behavior of the Eudragit RL100 NPs toward a model water/oil interface, using a  
46 dynamic tensiometer with axisymmetric drop shape analysis. The study investigated the NPs'  
47 adsorption, as well as their rheological behavior. The aim of this part was to reveal the main  
48 phenomena that govern the interactions between NPs and the interface in order to understand  
49 the origin of Pickering nano-emulsions' stability. The last part of the study was concerned  
50 with the stability and *in vitro* release of a model encapsulated drug (ketoprofen) in a gastric  
51 and simulated intestinal environment. The results showed that Pickering nano-emulsions  
52 significantly improved the resistance to gastric pH, inducing a significantly slower drug  
53 release compared to classical nano-emulsions' stabilized surfactants. These Pickering nano-  
54 emulsions appear as a promising technology to modify the delivery of a therapeutic agent, in  
55 the function of the pH, and can be, for instance, applied to the oral drug delivery of poorly  
56 soluble drugs.

57

58 **Keywords:** Pickering, nano-emulsion, Eudragit RL100, nanoparticle, ketoprofen.

59

## 60 1- INTRODUCTION

61 Pickering's solid particle-stabilized emulsions were discovered by Ramsden and Pickering in  
62 the 1900s and developed slowly until the 1980s [1,2]. Compared to surfactant-stabilized  
63 emulsions, Pickering emulsions have shown the advantages of strong stabilization and very  
64 good coalescence resistance due to the formation of a dense shell of solid particles  
65 irreversibly adsorbed around water droplet emulsions. Pickering emulsions also have the  
66 advantage of being nontoxic and environment-friendly and lower production costs [3–12].  
67 Over the past decade, Pickering emulsions have generated considerable interest in research in  
68 several areas—particularly in the cosmetic and pharmaceutical fields or food applications,  
69 where surfactants often have undesirable effects (such as irritation and hemolytic behavior)  
70 [13]. As a new drug delivery system, Pickering emulsions could facilitate dermal drug  
71 delivery [14,15], increase the oral absorption of poorly water-soluble drugs [16,17] and to  
72 improve the drug stability [18].

73 Recently, various Pickering nano-emulsions have been described [19–23]. They have average  
74 droplet diameters in the range of 50 to 300 nm. [24,25] Such fine droplets mean that creaming  
75 or gravity sedimentation becomes negligible, even over relatively long time scales. In  
76 addition, the much larger surface area of the droplets leads to more active formulations  
77 potentially advantageous for cosmetics [22], agri-food products [26,27], drug administration  
78 [21] and food manufacturing applications [19,28,29].

79 The adsorption of solid particles at the water/oil interface is irreversible and strong. It leads to  
80 the formation of a dense film and creates a barrier around the droplets, thus making the  
81 nanodroplets extremely resistant to coalescence. The control of the properties of the  
82 stabilizing particles due to the nature of the continuous phase can induce a change in the  
83 wettability, and can therefore possibly provide a control of the droplet interface  
84 destabilization and potentially a continuous release of drug. Energy related to the interactions  
85 of the NPs with the interface, *i.e.* adsorption and desorption, is related to their respective  
86 wetting by water and oil at interface [22]. Although the mechanisms involved in the stability  
87 of Pickering emulsions are well described, the role the the nature of the particles and their  
88 interfacial properties is still the subject of various opinions [30–33]. In some literature  
89 reports, it has been shown that submicron particles, in some cases, only exhibit a limited  
90 effect on the interfacial tension. Thus, they are rather considered a third phase located  
91 between water and oil, with a negligible role on the interfacial energy [34]. To study the

92 stability of foams, Hunter *et al.* [34] studied in parallel the adsorption of hydrophobic silica  
93 particles (~260 nm) and surfactants, onto an air/water interface. In that case, the NPs did not  
94 impact on the value of the surface tension [34]. However, other authors have reported an  
95 important effect of the particles on the interfacial tension. Kutuzov *et al.* [31], for instance,  
96 showed that interfacial tension decreased with increased particle concentration, using  
97 cadmium selenide (CdSe) particles at the toluene/water interface. In general, in the function  
98 of the nature of the particles and the experimental conditions, nanoparticles (NPs) in  
99 suspension can have a significant impact on surface tension or can be almost neutral [30–  
100 33,35–37]. In the case of Pickering emulsions, several types of NPs were shown to be very  
101 efficient stabilizers –such as CdSe NPs (1–8 nm) [38], silver NPs (1–5 nm) [39] or clay  
102 particles (25–35 nm) [40]. The drop tensiometer is widely used to study the interfacial  
103 tension and rheology of surfactant systems at liquid/liquid interfaces. It is interesting to note  
104 that the debate on the interfacial effect and activity of NPs at liquid/liquid interfaces is still  
105 ongoing, regarding whether they do not induce any modifications of the interfacial tension  
106 and rheological properties after their adsorption [30–33,35–37] or their adsorption strongly  
107 modifies the interfacial properties [41–44]. In fact, this debate might be likely due to the  
108 infinite variabilities of the NPs' chemical and physicochemical properties.

109 The main goal of this study was to develop Pickering nano-emulsions stabilized by  
110 Eudragit RL100 NPs as effective oral drug delivery systems. The choice of Eudragit RL 100  
111 was done because it is widely used for *in vivo* formulations intended to the oral route, and it  
112 is stable towards the physiological conditions encountered in the gastro-intestinal tract. To  
113 achieve this aim, we used a polymeric stabilizer to formulate a new form of Pickering nano-  
114 emulsions. As a model encapsulated drug, ketoprofen has been solubilized into the internal  
115 phase of the nano-emulsions. This formula was intended to prolong the effect of ketoprofen  
116 and thus reduce the frequency of administration. In addition, we studied the effect of NPs on  
117 interfacial tension. In parallel, the study of the NPs' adsorption onto a model oil/water  
118 interface was carried out on a drop tensiometer. This experimental approach provide the  
119 kinetics of the NPs' adsorption and allow accessing the rheological properties of the NPs  
120 monolayers. Interfacial rheology experiments were performed to characterize the phenomena  
121 governing the particle adsorption at the interface and understand the strength of their surface  
122 activity and their efficiency to stabilize the nano-emulsion droplets' interface. Further  
123 characterizations were conducted to evaluate the nano-emulsion size and stability, along with

124 in vitro release studies of a model encapsulated drug (ketoprofen) performed in a simulated  
125 gastric and intestinal medium (pH 1.2 and 6.8, respectively).

126

127

## 128 **2- EXPERIMENTAL SECTION**

### 129 **2-1 Materials**

130 Ketoprofen was purchased from Fagron S.A (Saint-Denis, France), and Eudragit<sup>®</sup> RL100  
131 (Ammonio Methacrylate copolymer Type A NF) from Evonik Röhm GmbH Pharma  
132 Polymers (Darmstadt, Germany). Acetone and cyclohexane analytical grades and Kolliphor<sup>®</sup>  
133 ELP (nonionic PEGylated surfactant) were purchased from Sigma Aldrich. Medium chain  
134 triglyceride compatible with the parenteral administration, Labrafac<sup>®</sup> WL1349 was obtained  
135 from Gattefossé SA (Saint-priest, France), and pure water from a Millipore super-Q unit  
136 (Millipore, Illkirch, France). All chemicals used were of analytical grades and used without  
137 modification.

138

### 139 **2-2 Methods**

#### 140 2-2-1 Preparation of NPs Eudragit RL100

141 Nanoparticles were prepared by nanoprecipitation method [45]. Eudragit RL100 was  
142 dissolved in the internal phase containing acetone (50 mL) at room temperature (25°C). The  
143 ratio of organic phase in the aqueous phase was (3:1). The resulting organic phase was  
144 injected at the constant rate of 0.5 mL / min in aqueous phase (150 mL) containing 1% of  
145 Kolliphor<sup>®</sup> ELP, under a gentl agitation at 300 rpm. Acetone was then removed using a  
146 rotavapor.

147 The nanoparticle suspension is first concentrated by evaporating of a significant amount of  
148 water (75 mL) and then washed for 48 hours. The NPs are then washed with MilliQ water by  
149 dialysis Spectra-Por, regenerated cellulose, cutoff 8-12 kDa), in MilliQ water under gentle  
150 stirring, and for 48 hours. Dialysate was changed once after 24h. Objective of this washing  
151 stage is to remove the free surfactant (Kolliphor<sup>®</sup> ELP). These washed NPs suspensions were  
152 used to prepare the nanoemulsions.

153

### 154 2-2-2 Preparation of Pickering nanoemulsions

155 The O/W nanoemulsions were formulated with 80 wt.% of aqueous phase containing the NPs  
156 and 20 wt.% of Labrafac<sup>®</sup> WL1349 as oil phase. A premix is formulated using a mechanical  
157 mixer (Ultraturrax, IKA T-25 digital) operating at 22400 rpm for 3min, at 25 °C. Then, the  
158 nano-emulsion is generated by ultrasonication (Sonics Materials, Bio block 75043, Newtown,  
159 MA, USA), 150 W, watt and 20 kHz, during 3 minutes (6 cycles of 10 s “on” and 20 s “off”).

### 160 2-2-3 NPs Eudragit and Pickering nanoemulsions characterizations

161

#### 162 *2-2-3-1 Size distribution and $\zeta$ potential measurements*

163 Size distributions, polydispersity indexes (PDI) and zeta potentials were determined with a  
164 NanoZS (Malvern Instruments, Orsay, France), by dynamic light scattering (DLS), and  
165 measurement of the electrophoretic mobility of the nano-emulsion droplets, respectively. All  
166 experiments were performed in triplicate.

167

#### 168 *2-2-3-2 Transmission electron microscopy*

169 Transmission electron microscopy (TEM) characterization were performed using Philips  
170 Morgagni 268D microscope operating at 70 kV. No staining agent were used and the samples  
171 were diluted 100 times with MilliQ water. A drop of the sample, beforehand deposited on a  
172 support (carbon type-A, 300 mesh, copper, Inc. Redding, PA), was dried at 40°C.

173

#### 174 *2-2-3-3 Axisymmetric Drop Shape Analysis (ADSA)*

175 Interfacial properties were assessed by axisymmetric drop shape analysis using a dynamic  
176 drop tensiometer (Teclis, Longessaigne, France). The first experiment was the study of a  
177 rising drop (drop of cyclohexane in water) (8 microliters) maintained at constant volume and  
178 temperature. Aqueous phase was either the NPs 40 nm suspension) and MilliQ as control.  
179 The second type of experiment was the pendant drop configuration (drop of aqueous NPs  
180 suspension in cyclohexane. The interfacial tension was determined from the drop profile and  
181 analyzed using a CCD camera integrated to the setup. The drop profile results from a

182 competition between gravity and capillary forces tend to elongate the drop profile whereas  
183 the capillary forces (which depend on the interfacial tension) tend to round the drop profile.  
184 As a result, its Laplacian shape gave the values of interfacial area and surface tension. All  
185 experiments were performed at 25 °C, in triplicate.

186

#### 187 *2-2-3-4 Interfacial rheology*

188 The dilatational elastic modulus was assessed by the relationship between surface tension and  
189 interfacial area (imposed though a sinusoidal profile). The experiment begins when the  
190 surface tension is stabilized, and reproduced over a large frequency range (0.0033 Hz, 0.005  
191 Hz, 0.0066 Hz, 0.01 Hz, 0.016 Hz, 0.022 Hz, 0.033 Hz, 0.05 Hz, 0.066 Hz, and 0.1 Hz).  
192 Experiments were conducted in order to get Bond number around 0.2-0.25, and sinusoid  
193 amplitudes around 10% of the drop volume [46–48] . Temperatures was maintained at 20°C,  
194 and experiments were performed three times.

195

#### 196 *2-2-4 In vitro release study*

197 As a model drug soluble in oil, ketoprofen was encapsulated in Pickering nanoemulsions at  
198 0.33 mg/mL. The solubilization of ketoprofen in Labrafac® WL 1349 was carried out by  
199 using a thermomixer (Thermomixer C Eppendorf) at 37°C for 15 min. The ketoprofen release  
200 profiles were characterized by dialysis (2 mL of loaded nanoemulsions at a concentration in  
201 solution equal to 0.33 mg/mL, and the dialysis tubing as Spectra-Por, regenerated cellulose,  
202 cut-off: 12-14 kDa). Dialysis was done in 300 mL, magnetically stirred at 100 rpm. The first  
203 time period was fixed at 30 min in simulated gastric fluid at pH = 1.2 as a release medium.  
204 Then, 9 hours in PBS at pH = 6.8 [49,50]. Aliquots of 5 mL were regularly collected from the  
205 dissolution medium, and analyzed by UV spectrophotometry (UV 2400 PC series  
206 SHIMADZU spectrophotometer, Kyoto, Japan). Absorbance values were monitored in a  
207 quartz cuvette at 258.5 nm and 260 nm for simulated gastric fluid and PBS respectively. Sink  
208 conditions were maintained by replacing 5 mL of the release medium with fresh media at  
209 each sampling point. This allowed the determination of the cumulative drug amounts released  
210 from nanoemulsions. UV-vis absorption spectra of the Pickering nanoemulsions were  
211 recorded on sample solutions using a UV 2400 PC series SHIMADZU spectrophotometer



212 with a wavelength range of 180 – 500 nm at 0.2 nm sampling interval. All experiments were  
213 performed in triplicate.

214

### 215 **3- RESULTS AND DISCUSSIONS**

#### 216 **3-1 Characterizations of NPs and Pickering nano-emulsions**

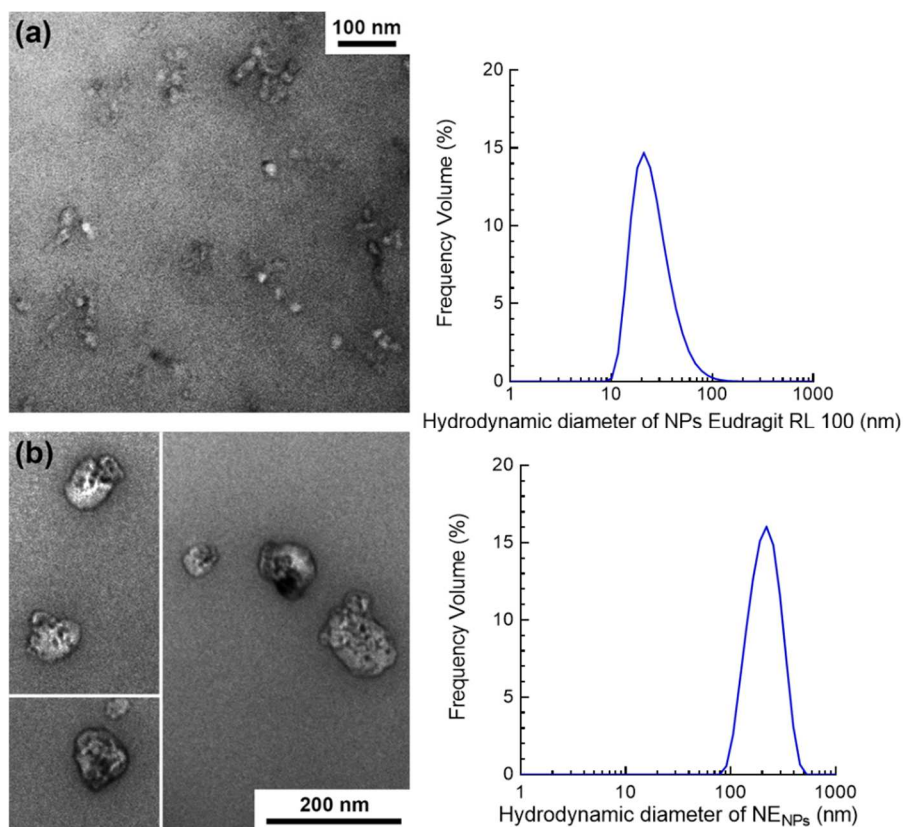
217 The size of the NPs depends on the composition of the aqueous and organic phases used  
218 during the preparation. Eudragit RL100 NPs were prepared and they showed a size  
219 distribution having a log-normal profile, centered on a diameter of 40 nm (see Fig. 1). The  
220 value of the polydispersity index (PDI) was equal to 0.098, which implied a good  
221 monodispersity of the suspension. Finally, the measured zeta potential was equal to +35 mV.

222 NPs of sizes 40 nm were formulated. The suspension of the NPs was used to prepare the  
223 Pickering nano-emulsions. A ratio (4:1) (suspension of NPs in Labrafac® WL1349) was used.  
224 The appearance of the formulation was transparent white. The manufacturing protocol was  
225 highly reproducible. The size of the Pickering NPs was an average of 220 nm. A good  
226 polydispersity index (0.184) was observed for the preparation (4:1). The zeta potential  
227 obtained was of the order of +35 mV and was the same as for the polymeric NPs prepared.  
228 Morphological characterizations of the NPs and nano-emulsions were performed by  
229 Transmission electron microscopy (TEM) (see Fig. 1). NPs (Fig. 1 (a)) appeared as round  
230 spheres with a size coherent with the dynamic light scattering (DLS) results and a distribution  
231 centered on a diameter of 40 nm. Some were isolated in the carbon support while others were  
232 aggregated as clusters. This usually happens during sample drying. As they were  
233 nanoprecipitated, the polymer NPs were in a glassy state and showed a hypo-contrast, which  
234 is generally the opposite of what happens in lipid particles [51]. On the other hand, nano-  
235 emulsions (Fig. 1 (b)) showed larger particles that were still in line with the DLS results  
236 (150–200 nm), and a hypo-contrast that is likely related to the presence of polymer particles  
237 at the droplet's interface.

238 These observations appear to be in coherence with the literature reports that have presented  
239 Pickering emulsions stabilized by solid particles [33,52]. Thus, it seems to corroborate the  
240 fact that the nano-emulsions formulated were effectively stabilized with Eudragit RL100  
241 NPs. Nano-emulsion droplets appeared well differentiated from each other, globally  
242 conserving their shape even after vacuum establishment during the TEM observations (*i.e.*

243 not spread onto the carbon support as reported with simple nano-emulsions [51]). This means  
244 that the interface was stabilized by aggregated NPs, creating a rigid film that acted as a  
245 physical barrier against flocculation and coalescence.

246



247

248 **Figure 1:** Physico-chemical characterization of the polymer nanoparticles (a) and Pickering nano-emulsions (b),  
249 by transmission electron microscopy (left row) and dynamic light scattering (right row).

250 These observations appears in coherence with the literature reports that presented Pickering  
251 emulsions stabilized by solid particles [33,52], thus seems to corroborate the fact that the  
252 nano-emulsions formulated are effectively stabilized with Eudragit RL100 NPs. Nano-  
253 emulsion droplets appear well differentiated each other, globally conserving their shape even  
254 after vacuum establishment during the TEM observations (*i.e.* not spread onto the carbon  
255 support as reported with simple nano-emulsions [51]). This means that the interface is  
256 stabilized by aggregated NPs, creating a rigid film that acts as a physical barrier against  
257 flocculation and coalescence.

### 258 **3-2 Interfacial coverage**

259 The coating of a spherical droplet with smaller NPs generally results in thick and compact  
260 shells [44,53–55]. To study and confirm this hypothesis, the surface coverage was followed

261 in the function of the volume fraction of the dispersed phase. The NP packing around a larger  
262 particle can be, in the function of the particle properties, either a compact monolayer [56] or a  
263 thick multilayer particle shell [57]. In this section, we propose studying the emulsion surface  
264 coverage by NPs, through a methodology that involves investigating the relationship between  
265 the size of the nano-emulsions formulated in the function of the volume fraction of dispersed  
266 phase (*i.e.* of oil) and estimating the emulsion coverage as the maximum number of NPs  
267 entrapped at the droplet interface. At constant NPs size and concentration in the aqueous  
268 phase, different Pickering nano-emulsions formulations were prepared by increasing the  
269 value of the volume fraction of the dispersed phase. The values of the nano-emulsion  
270 hydrodynamic diameter (as reported in Fig. 2 (a)) revealed the gradual increase of the nano-  
271 emulsion size –an expected result since the number of NPs is constant in the bulk. Then, the  
272 corresponding total number of nano-emulsion droplets  $N_{NE-tot}$  in the suspension (see  
273 Fig. 2 [b]) decreased initially but finally stabilizes as the oil volume further increased. As the  
274 additional dispersed phase was added, the total specific surface of the oil nano-emulsion size  
275 decreased and the number of particles fell. The stabilization means an equilibrium was  
276 reached and might be the sign of the total consumption of the NPs for the interface  
277 stabilization. This result is coherent with a lack of stabilizing agents, all NPs being already  
278 trapped at interface.

279 Therefore, assuming that at equilibrium, all the available oil/water interface is occupied by  
280 the NPs and trapped at the interface at their largest effective cross-section ( $S_{NPs}$ ), the number  
281 of NPs that can possibly adsorb on the nano-emulsion droplet interface,  $N_{NPs/NE-I}$ , is evaluated  
282 as the ratio between the area of a single nano-emulsion droplet  $A_{NE-I}$  and the section of a solid  
283 lipid NP  $S_{NPs}$  (see Fig. 2 (c)). Thus,  $N_{NPs/NE-I}$  increase with the volume fraction of the  
284 dispersed phase (an expected behavior as the droplet size increases) (Fig. 6 (a)). Finally, the  
285 total number of NPs adsorbed onto the nano-emulsions droplets,  $N_{NPs/NE-tot}$ , as reported in  
286 Fig. 2 (d), showed a constant increase with the further addition of oil. This means that  
287 maximum interfacial coverage was not reached even at the highest volume fraction.

288 The average droplet diameter is proportional to their coverage rate, and inversely  
289 proportional to the total number of stabilizing particles. A similar relationship between the  
290 final diameter  $D_f$  and the mass of particles has been proposed in literature [4], based on the  
291 assumption that the particles form a monolayer in a compact hexagonal stack at the water-oil  
292 interface.

293 The “limited coalescence” is a phenomenon that occurs when the interfacial area of all the  
294 droplets is much greater than the surface the stabilizing particles could cover. Accordingly, as  
295 the adsorption is irreversible, coalescence reduces the interface up to it is equal to the surface  
296 that the adsorbed particles can cover. Thus, if the volume fraction of dispersed phase is  
297 increased, the limited coalescence will govern the final stabilization droplet size.

298

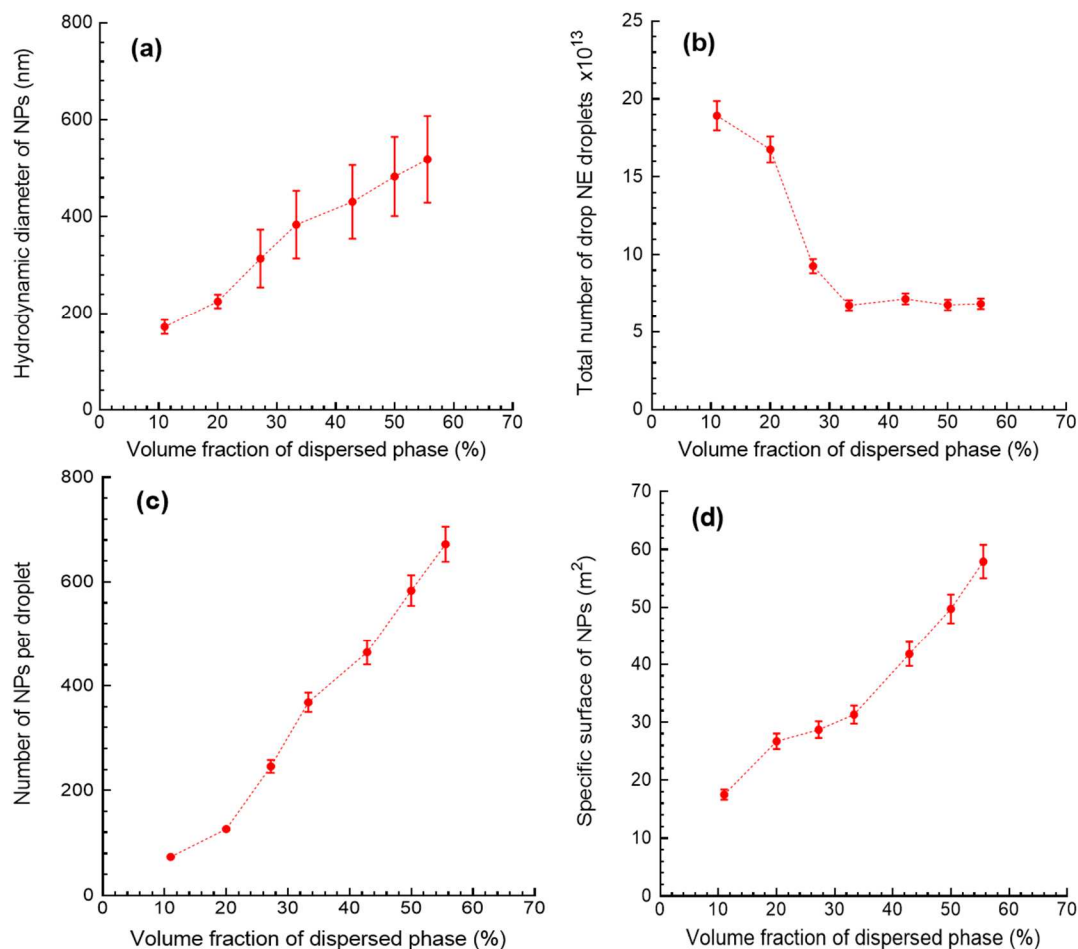
299 It follows, therefore, that the nano-emulsions formed were effectively stabilized by NPs,  
300 which is coherent with the idea that these Pickering nano-emulsions are stabilized by a dense  
301 NPs layer. This was confirmed by the TEM observations (Fig. 1 (a)), which showed an  
302 important concentration of Eudragit RL 100 NPs colocalized with the nano-emulsion  
303 droplets. Eventually, one can imagine such a layer constituting a barrier against the release of  
304 encapsulated active ingredients. These dialyzed NPs were characterized by tensiometry and  
305 interfacial rheology.

306

307

308

309



310

311 **Figure 2:** Study of the NPs coverage of the nano-emulsion droplets, in function of the volume fraction of  
 312 dispersed phase (continuous phase is water aqueous phase containing NPs, and the dispersed phase is oil  
 313 composed of MCT). (a) Hydrodynamic diameter of the nano-emulsions, (b) number of the nano-emulsion  
 314 droplets, (c) number of NPs adsorbed at the interface of a single nano-emulsion droplet, and (d) number of NPs  
 315 adsorbed onto all the nano-emulsions droplets,  $n=3$ .

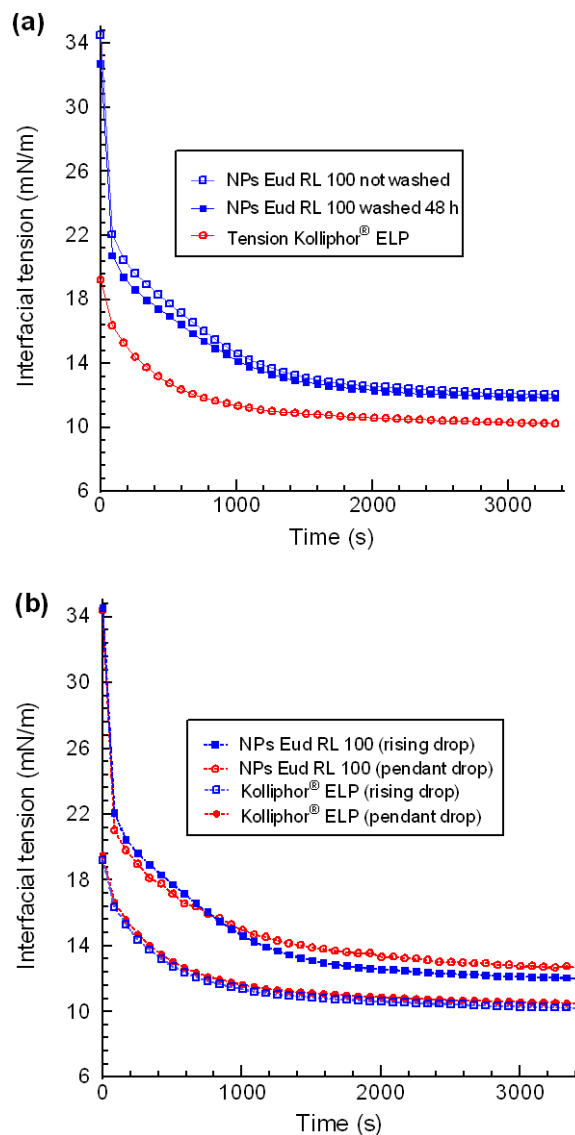
316

### 317 **3-3 Interfacial tension**

318 To better understand the stabilization mechanism of nano-emulsions, the adsorption kinetics  
 319 of polymeric NPs onto a model interface was studied. To this end, a model interface  
 320  $C_6H_{12}/water$  (aqueous NPs suspension) was created and the interfacial tension was followed-  
 321 up. The first control experiment was conducted to show that the interfacial effect is  
 322 effectively due to the NPs adsorbed at the interface and not the residual unwashed  
 323 surfactants. In this experiment (see Fig. 3 (a)), a concentration of  $5 \mu L/mL$  (*i.e.*  $5 \mu L$  of a  
 324 solution of NPs diluted in 1 mL of MilliQ water) of washed (*i.e.* before dialysis) and  
 325 unwashed (*i.e.* after 48 hrs of dialysis) NPs and surfactant (at  $3 \cdot 10^{-3} mg/mL$  – a concentration  
 326 corresponding to the one used in the NPs formulation) were compared (rising drop

327 configuration). The results showed that surfactant alone has a more important effect on the  
328 surface tension than the two other suspensions of NPs stabilized around 2000 s at 11 mN/m.  
329 On the other hand, washed and unwashed NPs suspension exhibited a very similar profile,  
330 also stabilized around 2000 s but slightly higher than the pure surfactant at about 2 mN/m. In  
331 fact, in the case of unwashed samples, both NPs and the free surfactants are liable to be active  
332 at interface. However, as the surface tension profile almost superimposed to the one of  
333 washed NPs, we can conclude that interfacial behavior is dominated by the NPS, *i.e.* the  
334 interfacial composition is predominantly composed of NPs. The second control experiment  
335 (see Fig. 3 (b)) compared the NPs to the free surfactant (at the concentration initially used for  
336 their formulation) in the cyclohexane rising and water pendant drop configurations. As  
337 expected, the values were close, irrespective of the configuration, and similar to those  
338 observed in Figure 3 (a). However, when the curves profiles were exactly superimposed for  
339 the surfactants, they appeared very slightly different regarding the NPs.

340



341

342 **Figure 3:** Study of the NPs adsorption of NPs on model  $C_6H_{12}$  / MilliQ water interface (aqueous suspension of  
 343 NPs) at 25°C. (a) Comparison of washed and not washed NPs (40 nm), and free surfactants (Kolliphor<sup>®</sup> ELP at  
 344  $3 \cdot 10^{-3}$  mg/mL), for the rising drop configuration. (b) Comparison of NPs (40 nm) washed, and free surfactants  
 345 (Kolliphor<sup>®</sup> ELP at  $3 \cdot 10^{-3}$  mg/mL), for pendant and rising drop configurations.

346

### 347 **3-4 Interfacial dilatational viscoelasticity measurement**

348 Dilatational viscoelasticity was performed according to the similar experimental  
 349 configuration used for the surface tension measurements at the water/cyclohexane interface  
 350 and the concentrations mentioned in the previous section with washed NPs. Pendant and  
 351 rising drops were also compared. This experiment, through the evaluation of the complex  
 352 dilatational elasticity  $E^*$  (with  $E^* = E' + iE''$ ), will provide the values of the conservative  
 353 ( $E'$ ) and dissipative ( $E''$ ), globally referring to the intermolecular interactions at the interface  
 354 and the interactions of the molecules at the interface with the subphases, respectively. These

355 data were obtained by imposing a sinusoidal variation of the volume on the drop and  
356 measuring the response of the drop as regards the surface tension (beginning after the  
357 stabilization shown in Fig. 3) for the rising drop.

358 To analyze these results and understand the limiting phenomena, the classical Lucassen and  
359 van den Tempel (LvdT) model was applied. LvdT is widely described in the literature [52–  
360 54] and accounts for a system in which the diffusion is the limiting process governing the  
361 interactions with the interface, that is, interfacial adsorption and desorption are slower and/or  
362 stronger than interactions at the interface between adsorbed compounds. LvdT is validated  
363 when both conservative and dissipative contributions satisfy the following equations:

$$364 \quad E' = E_0 \frac{1+\Omega}{1+\Omega+\Omega^2} \quad (\text{Eq. 1})$$

$$365 \quad E'' = E_0 \frac{\Omega}{1+\Omega+\Omega^2} \quad (\text{Eq. 2})$$

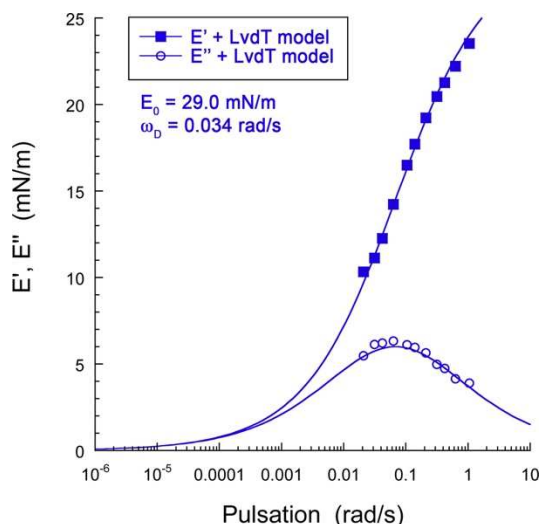
366 where  $E_0$  is the limit elastic modulus at very high frequency (for which the area increases  
367 only “dilutes” the NPs at the interface),  $\Omega$  is the reduced angular frequency given by  $\Omega =$   
368  $\left(\frac{\omega_D}{\omega}\right)^{1/2}$ , and  $\omega_D$  being the characteristic angular diffusion frequency representing the frontier  
369 between viscous friction regimes for  $\omega < \omega_D$  and elastic regime for  $\omega > \omega_D$ . The results are  
370 reported in Figure 4, showing the raw values of  $E'$  and  $E''$  along with the LvdT extrapolation.  
371 For comparison, similar experiments done in the pendant drop configurations were shown in  
372 the Supplementary Information section (Fig. S2).

373

374

375





376

377 **Figure 4:** Interfacial rheology study on the model water (containing NPs) / C<sub>6</sub>H<sub>6</sub> interface, rising drop  
 378 configuration. Experimental values of conservative ( $E'$ ) and dissipative ( $E''$ ) modulus are extrapolated  
 379 according to the Lucassen and van den Tempel model described by Eq. 1 and Eq. 2, respectively. and the limit  
 380 elastic modulus  $E_0$  and the characteristic angular diffusion frequency  $\omega_D$  are reported in the figures ( $n = 3$ ).

381

382 These results show a high impact of the pulsation on the values of the conservative  
 383 contribution  $E'$ . In comparison,  $E''$  shows more regular values around 5 mN/m. These  
 384 experimental data can be successfully modeled with the LvdT model, ( $R^2 = 0.995$  and  
 385  $0.926$ , for  $E'$  and  $E''$ , respectively), giving a limit elasticity value  $E_0 = 29.0$  mN/m and a  
 386 characteristic angular diffusion frequency  $\omega_D = 0.034$  rad/s. This concordance confirms that  
 387 the NPs are relatively mobile, able to migrate from the interface to the bulk surrounding  
 388 subphases, and the diffusion is effectively the limiting phenomenon. In fact, during the  
 389 surface expansion of the droplet, adsorption of additional NPs is allowed on the free  
 390 interfacial regions; and as the droplet contract, the NPs are gradually expelled. In the present  
 391 case, only adsorption/desorption phenomena dominated. We can also consider that NPs do  
 392 not form aggregate or cluster each other when they are confined at the interface (or if any,  
 393 only with loose interactions).

394 The bridge with the stability of Pickering nano-emulsion come with the confirmation of the  
 395 marked adsorption of the NPs at the droplet interface (during the sonication and the droplet  
 396 formation), first revealed by an impact on the surface tension, and then by the fact that the  
 397 NPs mobility toward interface is the main phenomena driving their interfacial behavior. On  
 398 the other hand, increasing the frequency strongly increases the conservative elasticity,  
 399 tending to  $E_0 = 29.0$  mN/m. In those conditions, the NPs are retained at the interface because  
 400 their diffusion is not fast enough to counterbalance the adsorption energy. However, after the

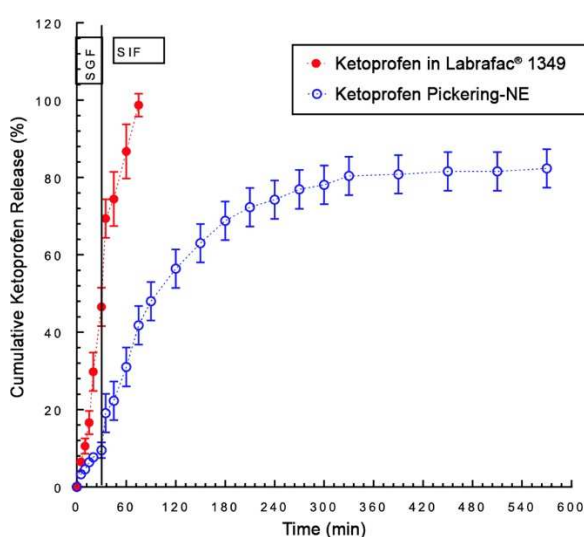
401 formulation of nano-emulsions (i.e., once the droplets are formed and ultrasonication  
402 stopped), we can consider the system below the elastic regime ( $\omega < \omega_D = 0.034$  rad/s),  
403 without further change in the droplet area, and the adsorption energy stably anchoring the  
404 NPs at the interface.

405 Interestingly, when the rheological behavior is compared to the pendant drop configuration  
406 (Fig. S2 in the *Supplementary information* section), the interfacial behavior is partly similar  
407 and the LvdT model can be also applied with some differences. The first one lies in the LvdT  
408 parameters values, very close for  $E_0$ , arising equal to 27.3 mN/m for pendant drop (and was  
409 29.0 mN/m for rising drop), but divided-up for  $\omega_D$ , equal to 0.016 rad/s for pendant drop (and  
410 was 0.034 rad/s for rising drop). On the other hand, for the lower frequencies  
411 ( $\omega < 0.042$  rad/s), the values of  $E'$  and  $E''$  literally shows a jump (indicated by arrows in  
412 Fig. S2) that makes these conditions out of the LvdT model, and that is important since it  
413 means that the diffusion is not anymore the NPs limiting process driving the interfacial  
414 phenomena but that NPs now strongly interact each other. When at the molecular level the  
415 interfacial curvature cannot have any influence on the interfacial phenomena, when  
416 increasing the scale with NPs sizing above 200 nm, it appears important. In addition, as the  
417 polymeric NPS herein studied stabilized oi-in-water nano-droplets, their location at the  
418 water/oil interface is are likely shifted towards water, meaning that the rising configuration  
419 (oil-in-water) is favorable and the pendant configuration (water-in-oil) is unfavorable.  
420 Unfavorable, revealed in Fig. S2, means that their confinement is increased, results in the  
421 creation of strong interparticle interactions when the interfacial deformation is slowest (*i.e.*  
422 when LvdT model is not verified). This interesting detail disclose the fact that NPs able  
423 nevertheless able to create a strong network, but when stabilizing the nano-emulsions is  
424 seems not effective, along with being an efficient stabilizing agent for nano-emulsions.

### 425 **3-5 In vitro release studies**

426 The choice of Eudragit<sup>®</sup> RL 100 in the fabrication of the stabilizing NPs was made because  
427 of their ability to form a strong barrier against the release of ketoprofen over time and the  
428 sensitivity of the polymer to the pH—the potential to induce a controlled release as a function  
429 of the location in the gastrointestinal tract. Ketoprofen an acidic drug with a pKa of 4.45,  
430 ketoprofen has poor aqueous solubility in acidic media (0.13 mg/ml at pH 1.2) [61,62], and  
431 considerably higher solubility at neutral environment (40.76 mg/ml at pH 6.8) [63]. As  
432 reported in Figure 5, the ketoprofen release is overall rapid—100% of the drug was released

433 within 2 h. By comparing the Pickering nano-emulsions and the control (ketoprofen in  
434 Labrafac<sup>®</sup> WL 1349 at the same concentration), it clearly appeared that the stabilization by  
435 Eudragit RL100 NPs significantly prolonged the ketoprofen release. In fact, for the control  
436 emulsion, 100% of the drug was leaked after only 1 h, while for Pickering nano-emulsions  
437 about 30% was leaked, and only 10% released during the 30 min at pH 1.2, with a gradual  
438 increase in the release rate at pH 6.8. Approximately, 70% of the drug has leaked after 5 h at  
439 pH 6.8, finally reaching 82% after 6 h. A cutting-edge effect on the drug release profile was  
440 obtained due to the stabilization of the nano-emulsion droplets by pH-sensitive NPs, which is  
441 in line with the objective of this study, opening the way for designing innovations in  
442 controlled drug release dosage forms [55,64,65].



443  
444 **Figure 5:** The release of ketoprofen encapsulated in the Labrafac<sup>®</sup> WL 1349 (red curve), and compared with  
445 Pickering nano-emulsions (blue curve: 80 wt.% of aqueous phase containing the NPs and 20 wt.% of Labrafac<sup>®</sup>  
446 WL1349; concentration of ketoprofen in the solution equal to 0.33 mg/mL). The first part presents a release in  
447 SGF (pH 1.2) followed by SIF (pH 6.8) as indicated in the figure.

#### 448 449 **4- CONCLUSION**

450 This study suggests a new formulation of nano-emulsions stabilized solely by Eudragit  
451 RL100 NPs. Solutions for formulating Pickering nano-emulsions have been found—that is,  
452 lipid droplets only stabilized with polymeric NPs (Eudragit<sup>®</sup> RL100). Pickering nano-  
453 emulsions are safe and very stable, but they are generally fabricated at a microscale. The  
454 formulation itself uses neither surfactants nor amphiphilic polymers, only NPs as stabilizers.  
455 This is the first innovation of this study. NPs generated by nanoprecipitation sized around  
456 40 nm and the nano-emulsions formulations around 220 nm showing high stability. The first  
457 part of this study focused on the characterization of these nano-emulsions to prove that they

458 are effective Pickering nano-emulsions and characterize the extents and limits of the nano-  
459 emulsion formulation process and the surface coverage in the function of the volume fraction  
460 of oil. The second part of the study focused on the interfacial behavior of the NPs at a model  
461 water/oil interface, analyzed through the axisymmetric drop shape analysis. The influence of  
462 the NPs on the surface tension and dilatational rheology was measured and the rheological  
463 behavior efficiently analyzed with the classical LvdT model. The results showed that the NPs  
464 were efficiently trapped at the oil/water interface; even for the control experiment in the  
465 presence of surfactants, the NPs had a predominant effect once trapped. The surface coverage  
466 revealed a compact layer surrounding the lipid droplets; this was confirmed by TEM. The  
467 application of the LvdT model to the rheology results also confirmed that NPs were  
468 efficiently adsorbed and that the adsorption/desorption predominated over interparticle  
469 interactions. This signifies that the NPs formed did not create an aggregated shell but were  
470 strongly anchored at the interface. Finally, we have shown that the release of a model  
471 lipophilic drug (ketoprofen) was significantly slowed down when nano-emulsions are  
472 stabilized with NPs, in comparison with surfactants used as the control. These last results  
473 fulfilled the objectives and specifications of the study, but the comprehensive  
474 physicochemical characterization carried out in this study opened new perspectives on the  
475 formulation of Pickering nano-emulsions.

476

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