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ABSTRACT

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

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

1- INTRODUCTION

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

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

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

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

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

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

2- EXPERIMENTAL SECTION

2-1 Materials

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

2-2 Methods

2-2-1 Preparation of NPs Eudragit RL100

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

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

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

2-2-3-4 Interfacial rheology

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

2-2-4 In vitro release study

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

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

3- RESULTS AND DISCUSSIONS

3-1 Characterizations of NPs and Pickering nano-emulsions

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

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

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

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

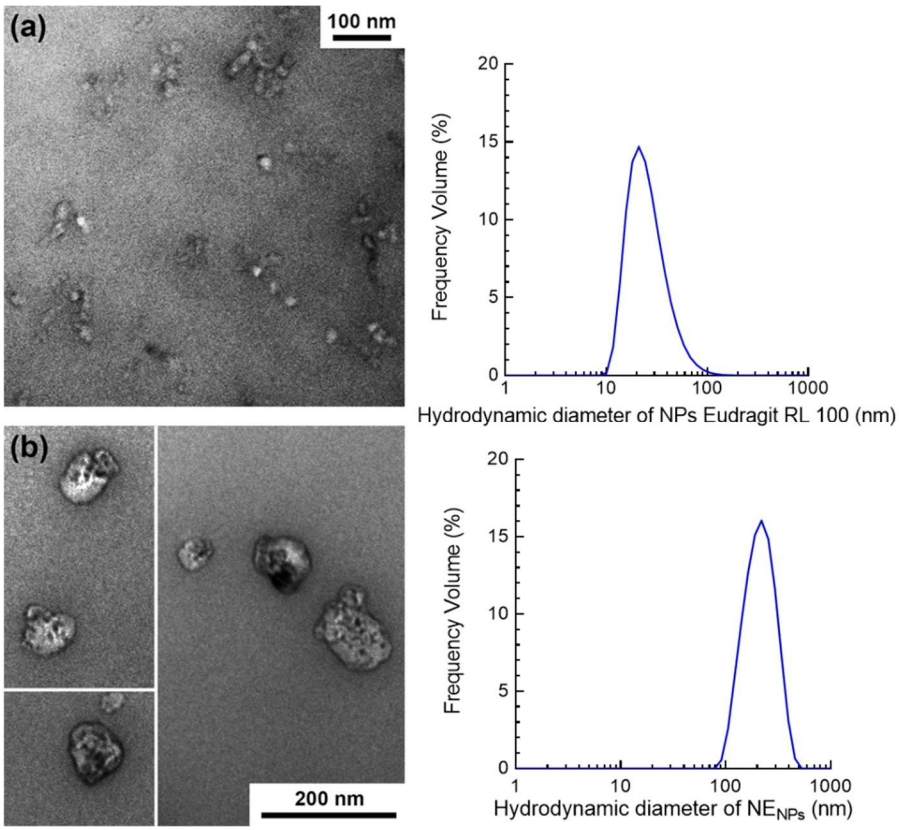

Figure 1: Physico-chemical characterization of the polymer nanoparticles (a) and Pickering nano-emulsions (b), by transmission electron microscopy (left row) and dynamic light scattering (right row).

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

3-2 Interfacial coverage

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

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

Therefore, assuming that at equilibrium, all the available oil/water interface is occupied by the NPs and trapped at the interface at their largest effective cross-section (S_{NPs}), the number of NPs that can possibly adsorb on the nano-emulsion droplet interface, $N_{NPs/NE\text{-}1}$, is evaluated as the ratio between the area of a single nano-emulsion droplet $A_{NE\text{-}1}$ and the section of a solid lipid NP S_{NPs} (see Fig. 2 (c)). Thus, $N_{NPs/NE\text{-}1}$ increase with the volume fraction of the dispersed phase (an expected behavior as the droplet size increases) (Fig. 6 (a)). Finally, the total number of NPs adsorbed onto the nano-emulsions droplets, $N_{NPs/NE\text{-}tot}$, as reported in Fig. 2 (d), showed a constant increase with the further addition of oil. This means that maximum interfacial coverage was not reached even at the highest volume fraction.

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

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

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

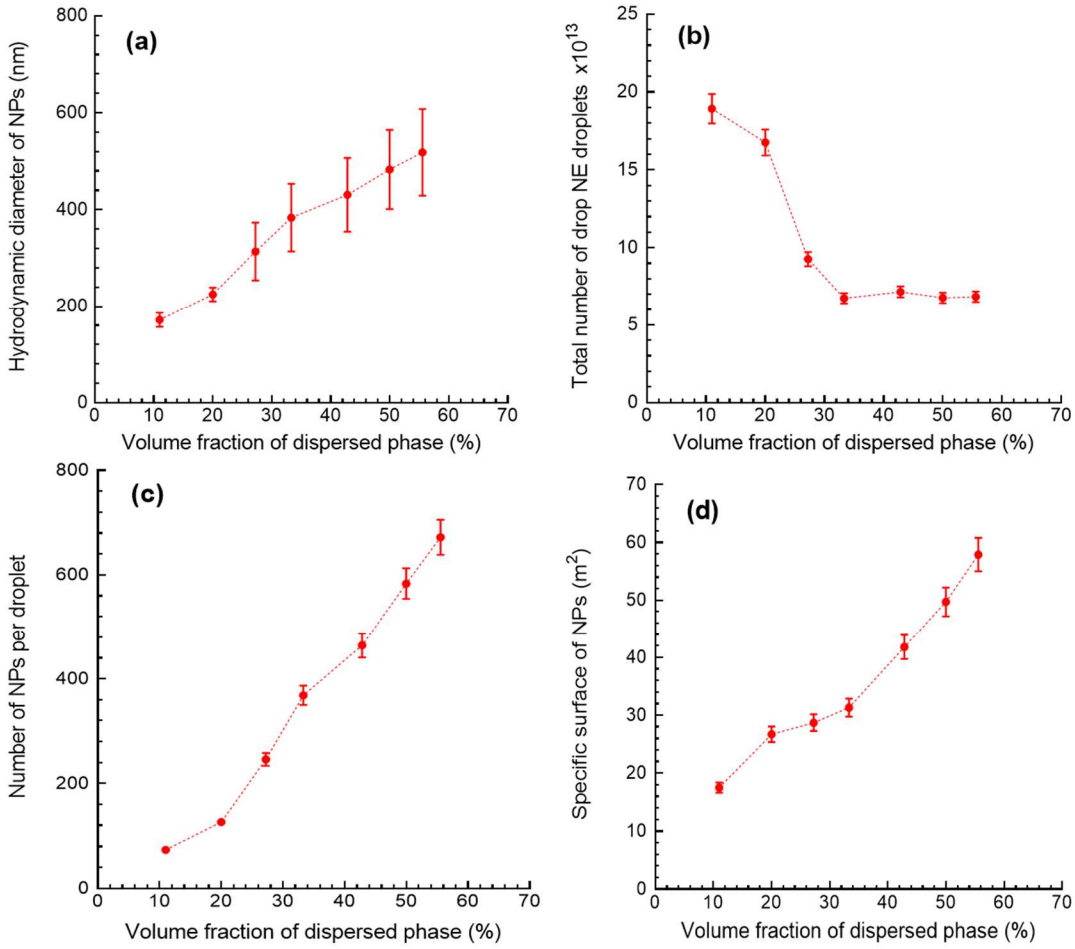

Figure 2: Study of the NPs coverage of the nano-emulsion droplets, in function of the volume fraction of dispersed phase (continuous phase is water aqueous phase containing NPs, and the dispersed phase is oil composed of MCT). (a) Hydrodynamic diameter of the nano-emulsions, (b) number of the nano-emulsion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

3-3 Interfacial tension

To better understand the stabilization mechanism of nano-emulsions, the adsorption kinetics of polymeric NPs onto a model interface was studied. To this end, a model interface C_6H_{12}/water (aqueous NPs suspension) was created and the interfacial tension was followed-up. The first control experiment was conducted to show that the interfacial effect is effectively due to the NPs adsorbed at the interface and not the residual unwashed surfactants. In this experiment (see Fig. 3 (a)), a concentration of 5 µL/mL (*i.e.* 5 µL of a solution of NPs diluted in 1 mL of MilliQ water) of washed (*i.e.* before dialysis) and unwashed (*i.e.* after 48 hrs of dialysis) NPs and surfactant (at 3.10^{-3} mg/mL –a concentration corresponding to the one used in the NPs formulation) were compared (rising drop

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

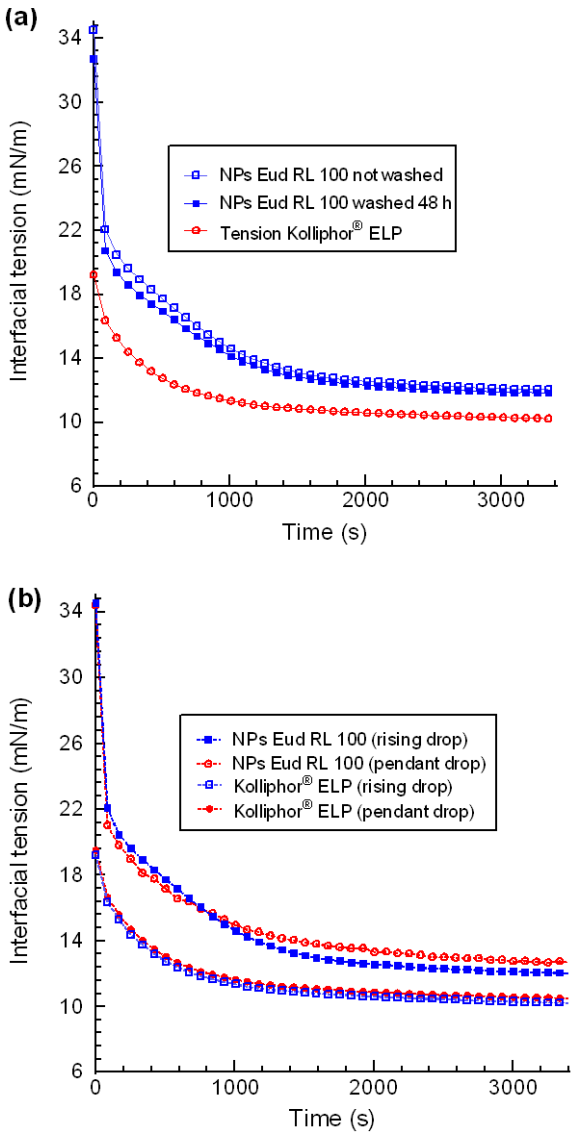

Figure 3: Study of the NPs adsorption of NPs on model C_6H_{12} / MilliQ water interface (aqueous suspension of NPs) at 25°C. (a) Comparison of washed and not washed NPs (40 nm), and free surfactants (Kolliphor® ELP at 3.10^{-3} mg/mL), for the rising drop configuration. (b) Comparison of NPs (40 nm) washed, and free surfactants (Kolliphor® ELP at 3.10^{-3} mg/mL), for pendant and rising drop configurations.

3-4 Interfacial dilatational viscoelasticity measurement

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

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

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

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

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

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

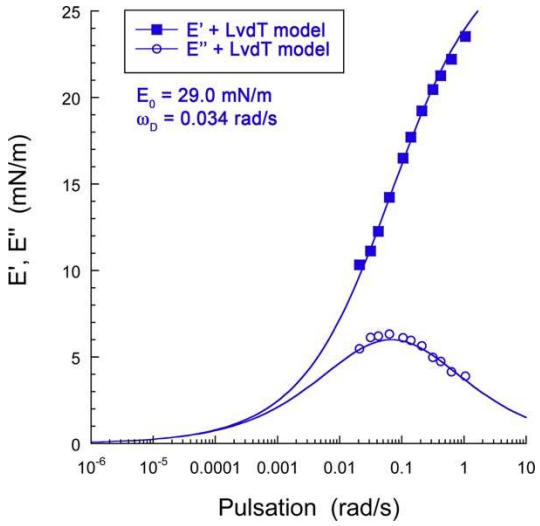

Figure 4: Interfacial rheology study on the model water (containing NPs) / C_6H_6 interface, rising drop configuration. Experimental values of conservative (*E'*) and dissipative (*E"*) modulus are extrapolated according to the Lucassen and van den Tempel model described by Eq. 1 and Eq. 2, respectively. and the limit elastic modulus E_0 and the characteristic angular diffusion frequency ω_D are reported in the figures (n = 3).

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

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

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

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

3-5 In vitro release studies

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

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

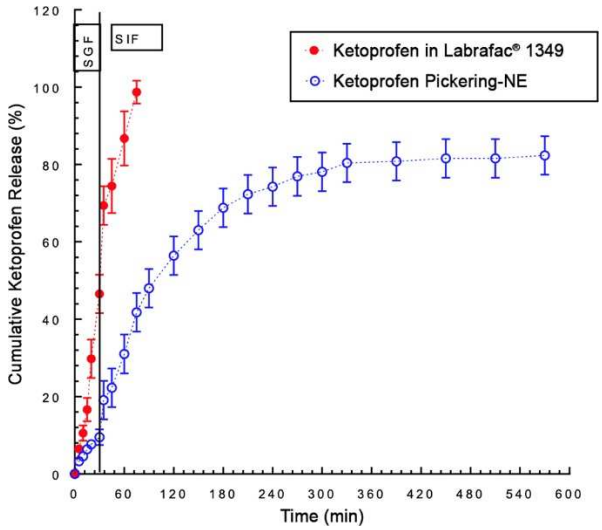

Figure 5: The release of ketoprofen encapsulated in the Labrafac® WL 1349 red curve), and compared with Pickering nano-emulsions (blue curve: 80 wt.% of aqueous phase containing the NPs and 20 wt.% of Labrafac® WL1349; concentration of ketoprofen in the solution equal to 0.33 mg/mL). The first part presents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

4- CONCLUSION

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

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

Acknowledgments

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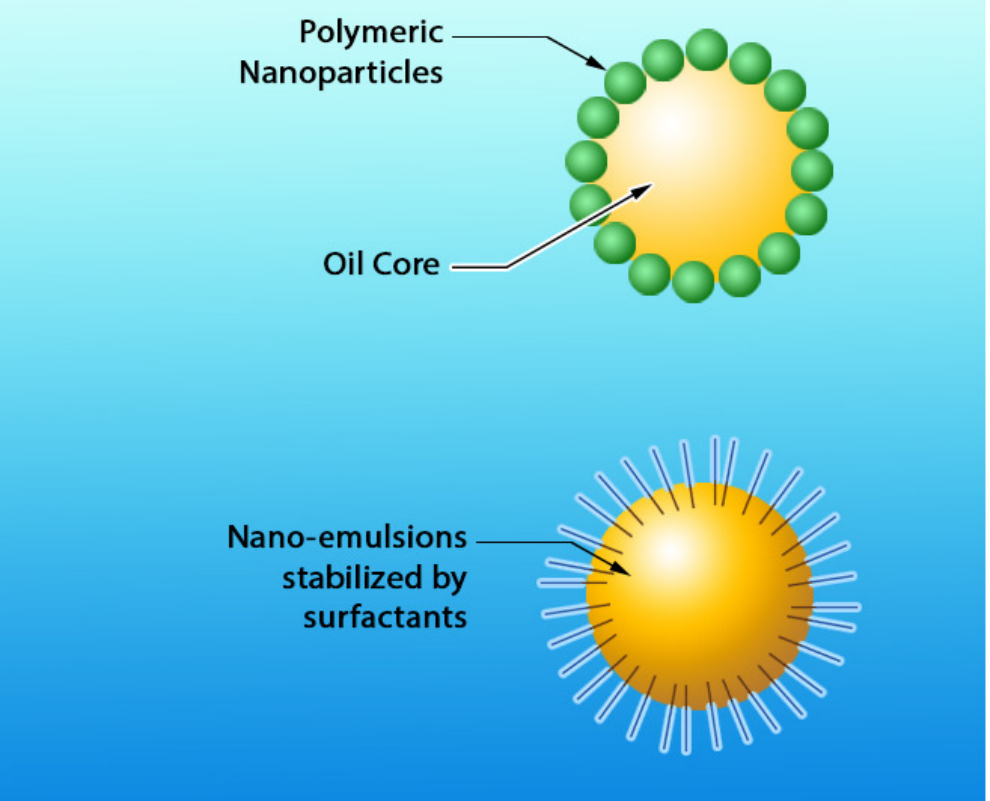
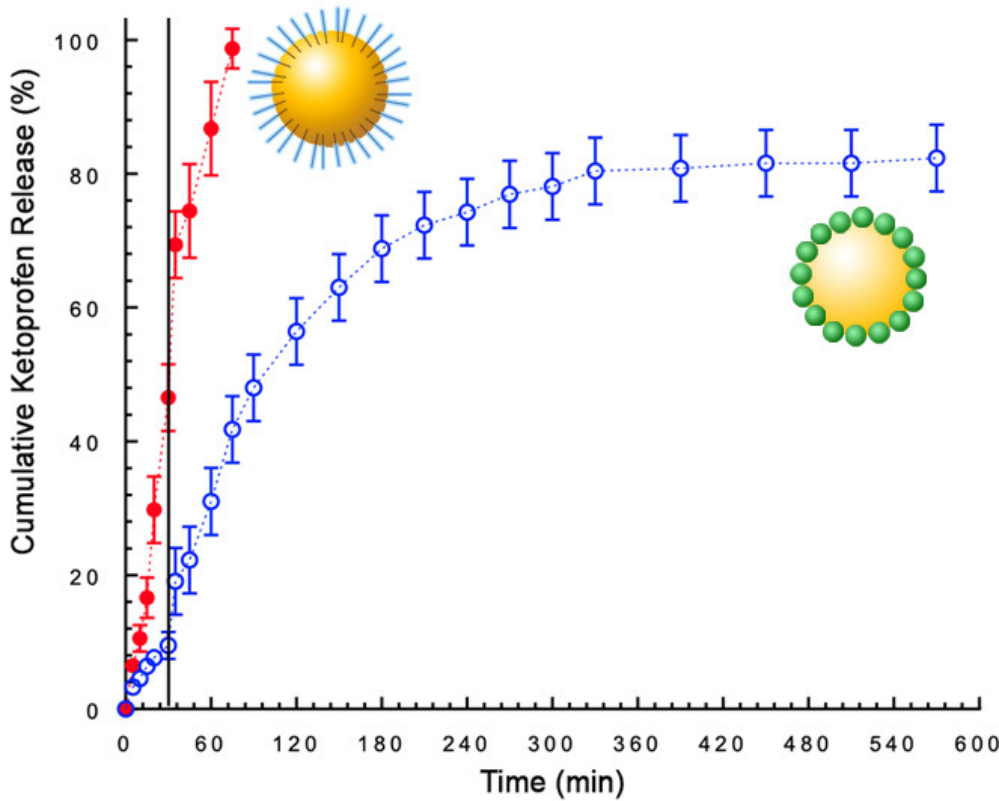

Polymeric
Nanoparticles
Oil Core
Nano-emulsions
stabilized by
surfactants


Cumulative Ketoprofen Release (%)
0
20
40
60
80
100
0
60
120
180
240
300
360
420
480
540
600
Time (min)