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► **To cite this version:**

Valentin Maingret, Clémence Courrégelongue, Véronique Schmitt, Valérie Héroguez. Dextran-Based Nanoparticles to Formulate pH-Responsive Pickering Emulsions: A Fully Degradable Vector at a Day Scale. *Biomacromolecules*, 2020, 21 (12), pp.5358-5368. 10.1021/acs.biomac.0c01489 . hal-03103695

HAL Id: hal-03103695

<https://hal.science/hal-03103695v1>

Submitted on 8 Jan 2021

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1 **Dextran-Based Nanoparticles to Formulate pH-Responsive Pickering** 2 **Emulsions: A Fully Degradable Vector at a Day Scale**

3
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15 16 17 **Abstract**

18
19 Biosourced Pickering emulsion stabilizers with stimuli responsiveness are mostly designed for
20 recycling and do not offer fast degradability as required for drug-delivery applications. Herein,
21 dextran – a hydrophilic and biofriendly polysaccharide obtainable from biomass recovery – was used
22 for the first time as a brick material for the formulation of (bio)degradable pH-sensitive Pickering
23 emulsions. It was first modified with hydrophobic acetals moieties to provide pH-sensitive acetalated
24 dextran. Under acidic conditions, it degrades into three biocompatible (macro)molecules: dextran,
25 ethanol and acetone. Nanoparticles of acetalated-dextran were obtained using the nanoprecipitation
26 process and could be similarly fully hydrolyzed under acidic conditions within 6 h. Then, O/W
27 Pickering emulsions of dodecane (model oil) and medium-chain triglyceride (biocompatible oil) were
28 successfully stabilized using these nanoparticles. pH-induced destabilization of these Pickering
29 emulsions (including nanoparticles degradation) took less than 24 h. Finally, neither accumulation of
30 nanoparticles nor harmful components release happened during the process, making this stimuli-
31 responsive vector safe and environmentally friendly.

32 33 **Keywords**

34
35 modified polysaccharide, stimuli-responsive, Pickering emulsions, bio-friendly vector, biocompatible
36 systems, nanoprecipitation.

37

1. Introduction

38
39

40 As surprising as it can be, mixing what is nonmiscible is at stake for a tremendous range of
41 technologies. Emulsions enable to disperse one phase in another one, the two phases being
42 nonmiscible. However, stabilizers must be introduced in the final formulation to ensure processability
43 and kinetic stability. Surfactants are widely used to fill this purpose but present major drawbacks such
44 as environmental toxicity and low stability efficiency¹.

45 Consequently, one can see the re-emergence of Pickering emulsions, observed more than a century
46 ago by Walter Ramsden in 1903² and by Spencer Umfreville Pickering in 1907³. Instead of molecular
47 surfactants, particles (ranging from dozens of nanometers to micrometers) are introduced and allow
48 steric stabilization of the interfaces. This kind of emulsion is more stable owing to the much higher
49 absorption energy⁴ of particles compared to surfactants and does not need a lot of stabilizing material
50 to achieve it, reducing toxicity.

51 Specifically, stimuli-responsive Pickering emulsions are of growing interest (from 0 to almost 60
52 papers/year in the last fifteen years, trend - rates estimated from Scopus) as they offer new
53 possibilities for various applications (medicine, cosmetics, agriculture and food)⁵⁻⁸. They benefit
54 from a high kinetic stability because of the particles anchoring at the droplets interface and can be
55 destabilized on demand under a stimulus (pH, temperature, specific reagent, light and magnetic
56 field⁹⁻¹³). Thus, if active compounds are encapsulated in the dispersed phase, they become available
57 for the target. Responsiveness of this kind of system mainly relies on a change of affinity of the
58 particles, allowing them to desorb thus leading to emulsion destabilization. To address the growing
59 needs of environment friendly materials, biosourced nanoparticles (CNC and starch) have been used
60 to stabilize pH-responsive Pickering emulsions¹⁴⁻¹⁷. No matter the strategy used to obtain pH-
61 sensitivity¹⁵ (leading to their desorption), (bio)degradation of these nanoparticles cannot be achieved
62 by the stimulus itself and thus would require very specific conditions and long delay. This is useful
63 for recyclability, but it may become an issue for drug-delivery-like applications because of their

64 potential accumulation and the unknown effects associated. One can note that chitosan is readily
65 sensitive to pH as it can undergo a sol-gel reversible transition^{18,19} but requires sharp control over pH
66 to be implemented and lacks kinetic tunability. Thus, to the best of our knowledge, no study has ever
67 considered Pickering emulsion stabilizers which could be fully degraded at a short time scale
68 (day/week) using only pH stimulus to do so.

69 In this respect, we developed new pH-responsive Pickering emulsions with (bio)degradable and bio-
70 sourced nanoparticles based on dextran. This system offers long time stability for storage but can be
71 destabilized within a day under acidic conditions, because of the hydrolysis of the stabilizing
72 nanoparticles. Degradation of the stabilizers and emulsion destabilization are then coupled because
73 the obtained (macro)molecular products can no longer stabilize the emulsion. Above all, these
74 products are biodegradable and of no consequence for the environment. Consequently, no
75 nanoparticles can accumulate, and all the produced materials are completely safe, making this new
76 class of stimuli-responsive Pickering emulsion stabilizers suitable for drug-delivery-like applications.
77 The raw material used to design such nanoparticles is dextran, a biosourced, biodegradable and
78 biocompatible hydrophilic polysaccharide²⁰. It is a by-product of the sugar industry and it can be
79 obtained from food wastes, promoting biomass recovery²¹. It is then cheap and obtainable from
80 renewable resources.

81 In the present paper, dextran was modified to produce acetalated dextran (Ace-dextran)²². This
82 modification can be undone under aqueous mild acidic conditions (pH 4.8), generating three
83 biocompatible products: dextran, acetone and ethanol. Using this material, nanoprecipitation was
84 performed to obtain for the first time Ace-dextran nanoparticles. We then successfully formulated
85 direct Pickering emulsions and observed the typical limited coalescence phenomenon²³. In the current
86 literature, the use of dextran to produce Pickering emulsion stabilizers is limited to the formation of
87 conjugate microgels²⁴. Thus, this is the first attempt to use dextran-only-based nanoparticles as
88 Pickering emulsions stabilizers. Finally, we proceeded with some destabilization attempts: first on
89 nanoparticles alone and then on the nanoparticle-stabilized emulsions. Nanoparticles are fully

90 hydrolyzed under acidic conditions, releasing simple and biocompatible materials: dextran, ethanol
91 and acetone. As a consequence of the nanoparticle degradation, the emulsions could also be
92 destabilized, with a slower kinetics.

93

94 **2. Experimental Section**

95 **2.1 Materials**

96

97 Dextran ($M_w=40\ 000\ \text{g/mol}$, $M_n=26\ 000\ \text{g/mol}$, $D=1.3$ as measured by the authors using Size
98 Exclusion Chromatography) and 2-ethoxypropene (95%) were purchased from ABCR. Anhydrous
99 dimethyl sulfoxide (DMSO, $\geq 99,9\%$) and dodecane (99%) were purchased from Sigma-Aldrich.
100 Triethylamine (TEA, 99%) was purchased from Fisher Scientific. Pyridinium-*p*-toluenesulfonate
101 (PPTS, 98%) was purchased from Fluka. Medium-chain triglyceride (MCT) “Miglyol 812N” was
102 furnished by Stéarinerie Dubois.

103 All reagents were used with no further purification unless noted. Solvents used are of analytical grade.

104

105 **2.2 Dextran modification to yield Acetalated-dextran (Ace-dextran)**

106

107 The dextran modification was adapted from the work of Kauffman et al.²². Typically, lyophilized
108 dextran (6.17 mmol relative to glucosidic units, 1 g) and PPTS (0.0617 mmol, 15.5 mg) catalyst were
109 dissolved into anhydrous DMSO (10 mL) before reaction with 2-ethoxypropene (37 mmol, 3.19 g)
110 under nitrogen gas (Figure 1) at 20°C. The reaction was quenched with 1 mL of TEA after 50 min
111 and reaction medium was then precipitated in basic water (pH 9, 0.02% v/v TEA/water), vacuum
112 filtered and lyophilized. The solid was then solubilized in absolute ethanol and centrifuged (10 min
113 at 11 000 rpm). Finally, the supernatant was precipitated in basic water (pH 9, 0.02% v/v TEA/water),
114 vacuum filtered and lyophilized to yield a white fluffy powder.

115 To characterize the final product, a suspension of Ace-dextran in D₂O (10 mg in 0.9 mL) was prepared
116 and 0.1 mL of D₂SO₄ was added to induce hydrolysis. A ¹H nuclear magnetic resonance (¹H NMR)
117 spectrum was recorded using a 400 MHz NMR instrument (Bruker 400 Ultra Shield) (Figure S1).
118 Three important peaks are then used to determine the modification rates: ethanol (produced from the
119 hydrolysis of an acyclic acetal), acetone (produced from the hydrolysis of a cyclic and an acyclic
120 acetal) and two hydrogens from dextran. Finally, peak integrations of acetone and ethanol can be
121 standardized for each glucose unit as described by Kauffman et al.²² and alternatively by Bachelder
122 et al.²⁵ to calculate the acyclic and cyclic modification ratios (Supporting Information SI.2). The
123 overall modification rate represents the number of substituted hydroxyl groups per 100 glucosidic
124 units.

125

126 Two syntheses with the same experimental conditions were carried out, they will be called S1 and S2
127 for clarity purpose and their characteristics are given in the Results and Discussion section.

128

129 **2.3 Nanoprecipitation of Ace-dextran**

130

131 Nanoparticles were produced through nanoprecipitation using a syringe pump (CHEMYX Fusion
132 101 Syringe Pump). Specifically, Ace-dextran was dissolved in tetrahydrofuran (THF) (5 g/L) and
133 injected in a 40 mL water bath at 0.4mL/min. At the end of this process, an additional 40 mL of water
134 was added to the dispersion, making an osmotic shock in the case of remaining good solvent into
135 aggregates. After concentration, the dispersion of nanoparticles was centrifuged (20 min at 11 000
136 rpm). The supernatant was discarded, and the nanoparticles were dispersed with basic water (pH 9,
137 0.02% v/v triethylamine/water) to prevent any early degradation. Nanoparticles were centrifuged
138 three times following the same process to eliminate potential residual free chains. Finally, the
139 recovered dispersion was concentrated using a rotary evaporator (40 °C bath) to eliminate water. The
140 concentrated dispersion can be stored several months without stability issues.

141 Two different nanoparticle dispersions were produced. They will be named NPD_x, where x stands for
142 the synthesis number of the Ace-dextran used for nanoprecipitation. Therefore, products from S1 and
143 S2 were used to produce NPD1 and NPD2.

144

145 The mass concentration of nanoparticles into dispersions was determined using the residual dry
146 weight technique.

147

148 Shape characterization of the nanoparticles was done by transmission electron microscopy (TEM) on
149 a HITACHI H-600 instrument (HV =75 kV). From TEM pictures and using ImageJ software, size
150 measurements of at least 100 nanoparticles were obtained, the volume-averaged diameter $D[4,3]$ of
151 nanoparticles was calculated following eq. 1:

$$152 \quad D[4, 3] = \frac{\sum_i^n d_i^4}{\sum_i^n d_i^3} \quad (1)$$

153 where d_i is the diameter of a nanoparticle from an n -nanoparticles population.

154

155 The size distribution of the nanoparticles and their average diameter (z in nm) were characterized by
156 dynamic light scattering (DLS) using a NanoZS90 instrument (Malvern Instrument Ltd, UK). The
157 wavelength used was 630 nm and the scattering angle set to 90°. The temperature was kept at 25 °C
158 unless noted. Systematically, three measurements of 10 runs (30 s each) were taken to ensure data
159 reliability. The concentration of the sample was low enough to avoid multiple scattering and is given
160 when necessary. Size distribution is characterized by an average diameter (z , in nm) and a typical
161 standard deviation (σ , in nm) or by the polydispersity index (PDI) calculated as follows eq. 2:

$$162 \quad PDI = \left(\frac{\sigma}{z}\right)^2 \quad (2)$$

163 Multi angle light scattering (MALS) measurements were performed using an ALV-5000 goniometer
164 with a He-Ne laser (633nm) and an ALV-5000/EPP multiple τ digital correlator (initial sampling time

165 of 125 ns). For static scattering six measurements of 5 s each were proceeded with an angle step of
166 5 ° from 50 ° to 150 °. The temperature of the toluene bath was kept to 20°C. Five samples with
167 decreasing concentrations were characterized (from 0.08 g/L to 0.008 g/L). Data acquired on ALV
168 correlator software were used to calculate the radius of gyration (R_g) and the molar mass of the
169 nanoparticles (M_w) using a Guinier Plot. Full calculations and methods are provided in the
170 Supporting information (SI.3,4,5,8,9 and Figure S6, S7 and S10).

171 Swelling of the nanoparticles was quantified by comparison of the average polymer density in the
172 nanoparticle (determined by MALS) to the density of free chains of similarly modified dextran at dry
173 state (1.37, determined by pycnometry). The proportion of absorbed water ($\%m_{water}$) with respect to
174 a nanoparticle dry mass (m_D) was defined as follows eq. 3: ²⁶

$$175 \quad \%m_{water} = \frac{m_w}{m_D} \quad (3)$$

176 Considering that the mass of a dry nanoparticle is equal to the mass of the polymer it contains and
177 hypothesizing ideal mixing, the previous relation can also be written as eq. 4:

$$178 \quad \%m_{water} = \frac{(V_S - V_D) * \rho_{water}}{V_S * \rho} \quad (4)$$

179 where V_S and V_D are the volumes of the nanoparticle in its swollen and dry state respectively and ρ
180 is the average polymer density in the swollen nanoparticle. Because of polymer mass preservation
181 $m_{polym} = m_D = V_S * \rho$. The geometrical radius from MALS measurements (median value between R_h and
182 R_g) was chosen to calculate V_S .

183 The water mass fraction content of a swollen nanoparticle can be then expressed as follows (eq. 5):

$$184 \quad \Phi_w^m = \frac{\%m_{water}}{1 + \%m_{water}} \quad (5)$$

185

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190 **2.4 Formulation of Pickering emulsions**

191

192 Emulsions were formulated using a water phase / oil phase (dodecane or MCT) ratio of 50/50 or 80/20
193 v/v with the total liquid volume set to 4 mL. A calculated amount of nanoparticle dispersion was
194 diluted into the pure aqueous phase to obtain the target concentration. Then the oil was added, and
195 the biphasic solution was stirred using an Ultra Turrax (IKA T25) at 20 000 rpm for 2 min with a
196 shaft (S25N 10G). Nanoparticles quantity is noted here as a concentration relative to the volume of
197 dispersed phase. As only O/W emulsions were formulated in this work, nanoparticle concentration
198 was related to the volume of oil (despite nanoparticles being unable to disperse in the oil phase). This
199 is meaningful because the volume of oil and the drop size define the total interfacial area to be covered
200 by the nanoparticles.

201 The water phase/oil phase ratio was set to 50/50 v/v to assess the kind of emulsion stabilized by the
202 nanoparticles (O/W or W/O). Once prepared, a small amount of the emulsion was taken and put in
203 two different vials containing water and oil, respectively. In the case of an O/W emulsion, the aliquots
204 dilute easily into water, not in oil. This is the reverse case considering W/O emulsions.

205 The emulsions were observed with an optical microscope (Zeiss Axioskop 40) in bright field using
206 x5 and x10 objectives. Pictures of the emulsions and of metric scales were taken using a digital camera
207 device linked to the microscope. From these, using the image treatment software ImageJ, size
208 measurements of at least 200 drops were obtained.

209

210 To describe the mean drop size of the emulsions, the Sauter diameter (eq. 6) was used:

$$211 \quad D[3, 2] = \frac{\sum_i^n d_i^3}{\sum_i^n d_i^2} \quad (6)$$

212

213 where d_i is the diameter of a drop from an n -drops population. The Sauter diameter is defined as the
214 surface-average diameter of the drops. Finally, to describe the drop size distribution width of the
215 emulsions, a typical standard deviation was calculated following (eq. 7):

$$216 \quad S = \sqrt{\frac{\sum_i^n (d_i - D[3,2])^2}{n}} \quad (7)$$

217
218 Cryo-SEM was performed on emulsion droplets to check the presence of nanoparticles at the interface.
219 A dodecane-in-water emulsion was formulated with the concentration of nanoparticles set to 6 mg/mL
220 of oil. The sample was observed without the use of a replica.

221 222 **2.5 pH-induced degradation of Ace-dextran nanoparticles**

223
224 A small amount of the nanoparticle dispersion was put in a DLS cuvette filled with freshly made
225 acetic buffer (pH 4.8) to obtain a slightly bluish dilute dispersion. The concentrations of nanoparticles
226 were set equal to 0.04, 0.08 and 0.16 mg/mL to determine the influence of concentration on the
227 degradation kinetics.

228 DLS analysis was immediately conducted after nanoparticles went in contact with the buffer. The
229 DLS cuvette was heated at 37 °C, which is the working temperature for many biological systems
230 including the human body. One measurement of 10 runs of 30 s was proceeded every 10 min during
231 a total time of almost 6 h.

232
233 From a DLS measurement, one can obtain the raw signal of the scattered signal named derived count
234 rate (DCR) in kilocounts per seconds (kcps). This signal intensity is directly related to the
235 concentration of diffusive entities in the sample (i.e., the nanoparticle concentration c_p) and their size
236 (z) (eq. 8)²⁷:

$$237 \quad DCR \propto c_p * z^6 \quad (8)$$

238 Both size and DCR were measured during the degradation. As the size of the nanoparticles did not
239 change, DCR was directly proportional to the concentration of nanoparticles (calibration curve of
240 DCR with various concentrations can be found in Figure S11). Thus, collecting the DCR data as a
241 function of time and normalizing them by the first obtained value allowed quantifying the
242 nanoparticles and therefore reporting their degradation ²⁷.

243

244 **2.6 pH-induced destabilization of formulated Pickering emulsions**

245

246 The same freshly made acetic buffer (pH 4.8) as for the degradation of nanoparticles was used.
247 Emulsions with a water phase / oil phase ratio of 80/20 v/v and a nanoparticle concentration of 6
248 mg/mL relative to the dispersed phase were prepared under the same conditions as described before.
249 For testing the emulsion destabilization, 2 mL of acidic buffer was added whereas 2 mL (the same
250 volume) of water was added in the control sample. Then both samples were kept at 37 °C on a shaker
251 plate at 50 rpm. Pictures of the emulsion cream were taken at regular time intervals to monitor
252 emulsion stability. Moreover, tiny aliquots of the emulsion cream were withdrawn to observe the
253 microscopic structure over time. We checked that this operation did not affect emulsion stability.

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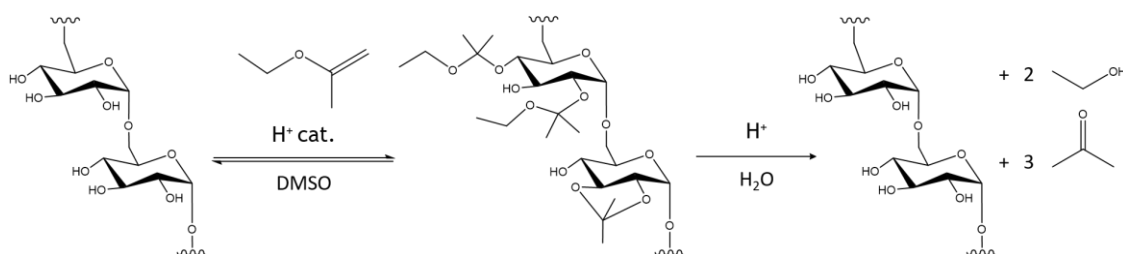
264 **3. Results and discussion**

265 **3.1. Dextran modification to yield Acetalated-dextran (Ace-dextran)**

266

267 Ace-dextran was prepared following the reaction scheme in Figure 1 at 20 °C. This dextran
268 modification led to the replacement of some hydroxyl groups of the glucosidic units by acetals which
269 can be either cyclic or acyclic. The number of acetals and their nature (cyclic or acyclic) were
270 determined by performing ¹H NMR on the totally hydrolyzed Ace-dextran.

271



272

273 *Figure 1. Reaction scheme for the formation of Ace-dextran with 2-ethoxypropene and its degradation in aqueous acidic medium*

274

275 *Table 1. Grafting Rates Determined by ¹H NMR*

Synthesis	S1	S2	Kauffman et al. ²²
Cyclic acetal rate	0.57	0.61	0.64
Acyclic acetal rate	0.98	1	0.99
Overall modification	213 %	223 %	227 %
Reaction temperature	20°C	20°C	Room Temp.

276

275 During hydrolysis, a cyclic acetal is cleaved into an acetone molecule whereas an acyclic acetal is
276 cleaved into an acetone and an ethanol molecule (Figure 1). By integrating methyl protons of acetone
277 (B, $\delta=2.2$ ppm Figure S1) and ethanol (C, $\delta=1.1$ ppm Figure S1) and normalizing them by the C₆

278 hydrogens from the dextran glucosidic unit (A, $\delta=3.9$ ppm Figure S1) one can determine the relative
279 grafting rate of cyclic and acyclic acetal onto dextran (Supporting Information SI.2).

280 Two batches of Ace-dextran were synthesized and then characterized by ^1H NMR after hydrolysis
281 (Supporting Information SI.2). Cyclic and acyclic acetal grafting rates obtained are summarized in
282 Table 1, and calculations are described in (Supporting Information SI.2).

283

284 **3.2. Nanoprecipitation of Ace-dextran**

285

286 **3.2.1 Nanoparticle Synthesis**

287

288 Ace-dextran nanoparticles were prepared through nanoprecipitation. This process has been
289 extensively used for the preparation of nanoparticles^{28,29}, including modified dextran-based ones³⁰⁻
290³². However, it is the first that time Ace-dextran (modified with ethoxypropene) nanoparticles are
291 obtained with this method. Kauffman et al.²² used the emulsion/evaporation process to produce
292 microparticles. Using this process, they had to introduce PVA (polyvinyl alcohol) chains to stabilize
293 the emulsion, which may remain in the final dispersion. As our goal is to use the particles to stabilize
294 emulsions, this could lead to biased results. Thus, as nanoprecipitation was done with no additional
295 stabilizer, the nanoparticle dispersion obtained was composed of only Ace-dextran. In addition, the
296 minimum size of Pickering emulsions droplets is intrinsically related to the size of the particles
297 anchored at the surface. Starting from microparticles would have shorten the field of possibilities.
298 Ace-dextran was solubilized in a good solvent and then added dropwise in an anti-solvent bath
299 solution (miscible with the good solvent). As the good solvent diffuses into the anti-solvent bath,
300 polymer chains start to collapse and associate to form spherical aggregates to yield nanoparticles
301 whose size is governed by the process parameters. The solvent used to solubilize Ace-dextran was
302 THF because it diffuses well in water and is easily removable by evaporation. This nanoprecipitation

303 process is in accordance with the requirements of green engineering and manufacturing as it avoids
304 the use of large quantities of energy and solvent.

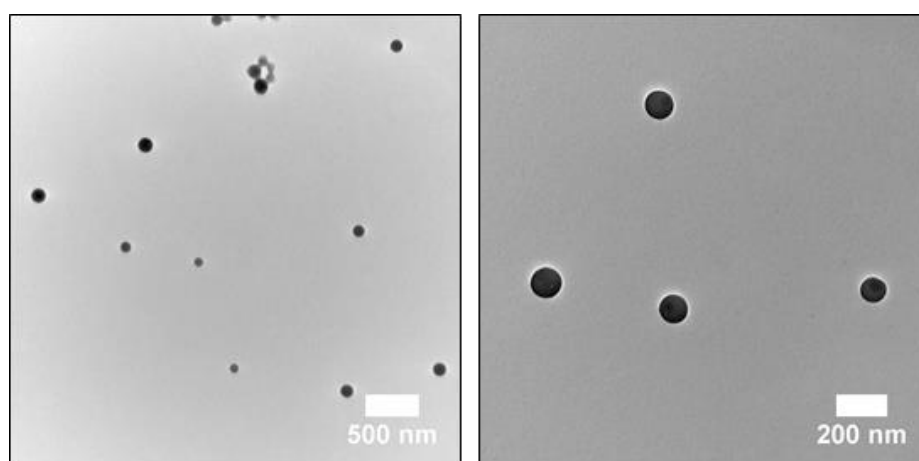
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306 **3.2.2. Nanoparticle characterizations**

307

308 TEM characterizations were performed on NPD1 nanoparticles to determine their shape. As shown
309 on Figure 2, the nanoparticles are spherical - making the following DLS measurements reliable - and
310 well defined. In addition, we were able to assess their size and found out a $D[4,3]$ of 122 ± 35 nm.

311



312

Figure 2. TEM images of nanoparticles from NPD1

313

314 According to DLS measurements, narrow size distribution of nanoparticles with an average
315 hydrodynamic diameter of around 200 nm was obtained (Table 2). The higher value obtained for
316 NPD1 nanoparticles (compared to TEM results) may be due to the different state of the nanoparticles
317 (in water vs dried under vacuum) and probably indicates that a swelling is occurring. This will be
318 discussed at the end of this part.

319

320

321

Table 2. Size distribution measurements obtained of NPD1 and NPD2 by DLS 90° and TEM

NPD (Measurement)	NPD1 (TEM)	NPD1 (DLS 90°)	NPD2 (DLS 90°)
Average diameter z (nm)	122 ± 35	220 ± 71	229 ± 61
PDI	0.08	0.105	0.072

322

323 To check the repeatability of the process, different nanoparticle batches starting from the same Ace-
 324 dextran synthesis were analyzed by DLS. All exhibited relatively the same size keeping a quite low
 325 PDI of 0.1 or below. This made possible to assemble different nanoprecipitation batches obtained
 326 from the same product without compromising narrow monomodal distribution.

327

328 Multi-angle static light scattering (SLS) was performed to calculate NPs gyration radius (R_g) and
 329 molar mass (M_w) in water (Supporting Information SI.5, Figure S6 and S7). From this, it was possible
 330 to calculate the average density of polymer in the nanoparticles (Supporting Information SI.8). The
 331 density of polymer in the particles will be required later in this work to calculate the coverage rate of
 332 the Pickering emulsion droplets by the nanoparticles. Results and relative standard deviations are
 333 given in Table 3.

Table 3. Multi angle SLS results using Guinier Plot and density calculation of the NPs from NPD1

R_g (nm)	M_w (g/mol)	ρ (g/mL)
89.64 (± 1.9 %)	1.384 10 ⁹ (± 1.08 %)	0.685 (± 15 %)

334

335 From these results, the swelling of nanoparticles into water could be appreciated. Indeed, the polymer
 336 density decreased from 1.37 (free chains – dry state) to 0.685 in the nanoparticle, meaning that the
 337 volume of a nanoparticle in water is twice the one of a “dry” one. The radius of a “dry” nanoparticle
 338 would be then equal to 147 nm, which follows TEM measurements results (122 ± 35 nm). In order to
 339 quantify the swelling of nanoparticles by water, proportion of absorbed water ($\%m_{\text{water}}$) was computed

340 according to eq. 4 and was equal to 0.73, indicating that the water mass fraction Φ_W^m (eq. 5) of the
341 nanoparticles is equal to 42%. Therefore, the nanoparticles are made of 42% weight of water and 58%
342 of the polymer.

343

344 **3.2.3. NP Stability**

345

346 Water dispersions of nanoparticles were stored in a transparent vial (to check turbidity or
347 sedimentation) protected from light during storage in a cupboard. No major destabilization
348 phenomenon occurred in more than 10 months, except slight but reversible sedimentation. This was
349 confirmed by size distribution measurements obtained by DLS at t_0 and $t_{10\text{months}}$ (Figure S12).

350

351 **3.3. Formulation of pH-sensitive Pickering emulsions**

352

352 **3.3.1. Emulsion type**

353

354 Emulsions of water phase/oil phase ratio 50/50 v/v were first formulated to assess the type of emulsion
355 stabilized. O/W emulsions were formed. Dodecane emulsions all creamed quickly because of the
356 large diameter of the droplets and the low density of dodecane (0.75 g.cm^{-3}) compared to water.

357

358 **3.3.2. Influence of nanoparticle concentration - Limited coalescence**

359

359 **phenomenon**

360

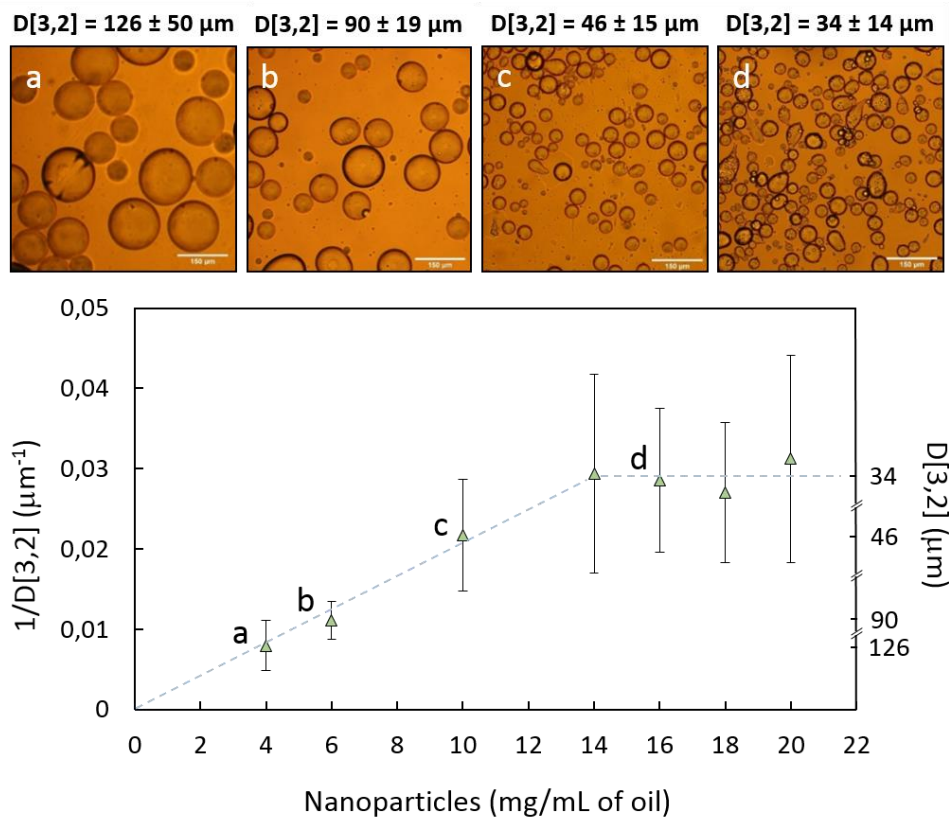
361 O/W Pickering emulsions were formulated varying the amount of nanoparticles (expressed as a
362 concentration of nanoparticles relative to the volume of the dispersed phase). We observed
363 microscopically that the average diameter of the droplets decreased when adding more stabilizing
364 material (low concentrations range). This phenomenon is typical of Pickering emulsions and is called
365 limited coalescence²³. Coalescence is in general a deleterious destabilization phenomenon but in this

366 case, one can take advantage of it - because it is limited - to produce narrow monomodal emulsions
367 ³³ with great re-feasibility. During the emulsification process, a large excess of interfacial area is
368 produced compared to the area that can be covered by the stabilizing nanoparticles. Consequently,
369 drops which are not enough covered coalesce to decrease the interfacial area. As the stabilizing
370 particles are irreversibly anchored at the interface, the coalescence phenomenon stops when the drops
371 are covered enough.

372 In this context, it has been proven that the inverted Sauter diameter of the droplets is linearly related
373 to the amount of nanoparticles used to stabilize them, as described in eq. 9 ³⁴:

$$374 \quad \frac{1}{D[3,2]} = \frac{c_p}{4C\rho_p d_p} \quad (9)$$

375 where c_p is the concentration of particles relative to the volume of the dispersed phase (oil – computed
376 from residual dry weight results), ρ_p is the particle density (here the average polymer density in the
377 nanoparticle ρ computed earlier), d_p is the geometrical particle diameter, and C is the surface coverage,
378 that is, the fraction of the droplet interfacial area covered by the particles. Using nanoparticles from
379 NDP1, we were able to observe this relationship for low concentrations, followed by a plateau (Figure
380 3). Detailed size measurements of Pickering emulsions are described in the Supporting Information
381 (Figure S13).



382

383 *Figure 3. Microscopic pictures of formulations with various concentrations: 4 mg/mL of oil (a), 6*
 384 *mg/mL of oil (b), 10 mg/mL of oil (c), 16 mg/mL of oil (d) – scale bar is equal to 150 μm (top) -*

385 *Evolution of $1/D[3,2]$ as a linear function of the nanoparticle (from NPD1) concentration, followed*
 386 *by a plateau (bottom)*

387 This linear relation is applicable for a range of low concentrations. At some point (beginning of the
 388 observed plateau), there are enough nanoparticles to fully stabilize drops formed by stirring. Then,
 389 no more coalescence can occur, and the drops diameter is set by the process (shearing source is
 390 responsible for area creation). As a result, there is no coalescence and the final size of the droplets
 391 will not change when adding more nanoparticles. Usually the emulsions, obtained out of the limited
 392 coalescence domain, are polydisperse as their size distribution directly result from turbulent stirring.
 393

394 From the slope of the linear domain of limited coalescence, one can obtain the surface coverage C of
 395 the oil droplets. Density and geometrical diameter of the particle used were determined using MALS

396 data (Figure S7). As a result, the calculated coverage is of 0.94 ± 0.14 (Supporting Information SI.8
397 Figures S9 and S10) which is close to that of a hexagonally close-packed narrow monomodal particles
398 organization at 2D where $C=0.9$ ³⁵.

399 Cryo-SEM experiments were performed to visualize the interface of dodecane-in-water emulsion
400 droplets. The concentration of nanoparticles used was 6 mg/mL (in the limited coalescence domain)
401 meaning that the coverage should be the same as the one calculated above. From the Cryo-SEM
402 picture (Figure 4), it can be deduced that the dodecane droplet is fully and densely covered with
403 nanoparticles. This is in good agreement with the coverage result deduced from optical microscopy
404 observations in the limited coalescence domain. Moreover, this close-packed organization may be
405 favored by the swelling state of the nanoparticles, probably making them softer and a little bit
406 deformable as they are composed of 42% of water. Thus, instead of spheres, it seems that some
407 polyhedrons can be distinguished on Figure 4. However, it is worth strengthening that swelling did
408 not induce nanoparticles sticking at the interfaces as no flocculation was observed.

409

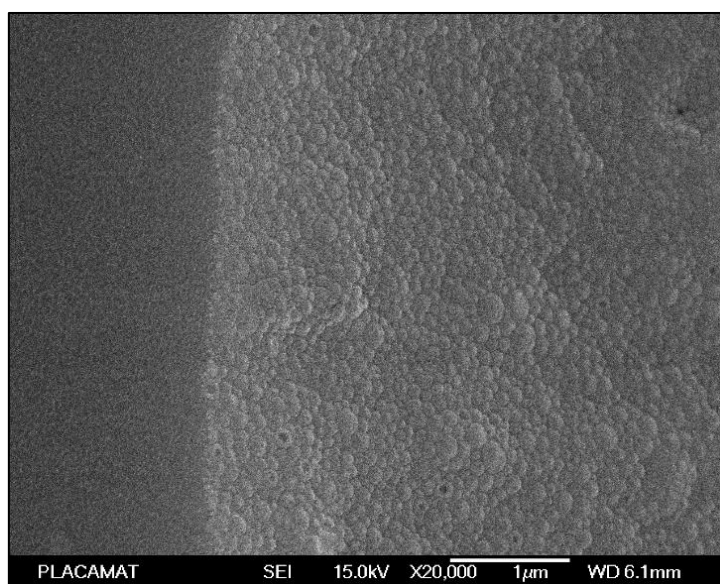


Figure 4. Cryo-SEM picture of the surface of a dodecane droplet in water stabilized by Ace-dextran nanoparticles (6 mg/mL of oil)

411 To summarize, nanoparticles of Ace-dextran can be used to formulate stable Pickering O/W emulsions
412 in a controlled way as the amount of introduced nanoparticles defines the final diameter of the oil
413 drops. The drops are densely covered by a monolayer of nanoparticles.

414

415 **3.4. pH-induced destabilization of formulated Pickering emulsions**

416

417 Assessment of the pH-induced destabilization of the formulated Pickering emulsions was done in two
418 main steps. First, pH-induced degradation kinetics of Ace-dextran nanoparticles suspended in water
419 was studied. Then, Pickering emulsions were subjected to the same acidic conditions to study the
420 destabilization mechanism and kinetics.

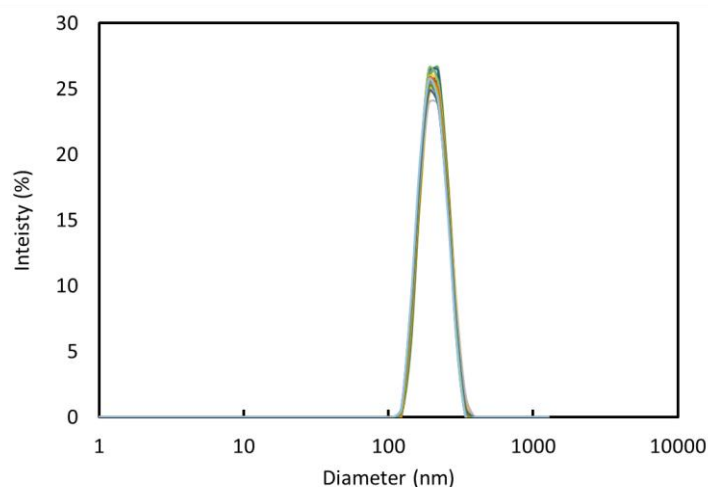
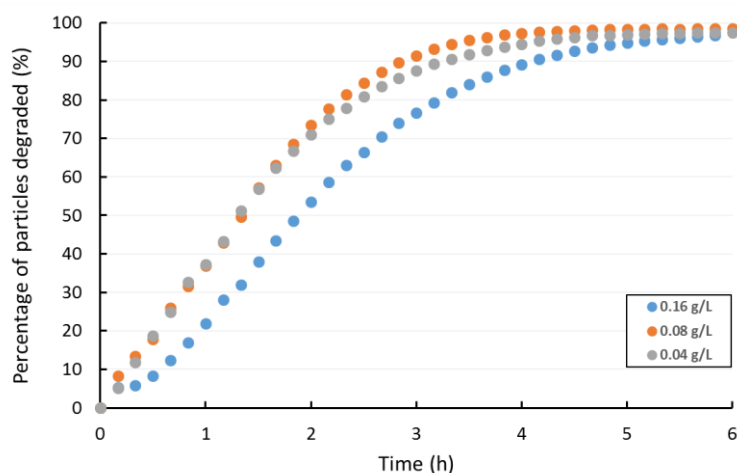
421

422

423 **3.4.1. pH-induced degradation of Ace-dextran nanoparticles**

424

425 Ace-dextran is hydrolyzed in aqueous acid medium, producing three fully biocompatible and
426 biodegradable products: dextran, ethanol and acetone. When assembled into nanoparticles the same
427 mechanism occurs and these nanoprecipitates finally tend to be solubilized into the acidic water
428 medium. DLS measurements of the nanoparticles from NPD1 in acidic medium were performed to
429 study the degradation kinetics. The DCR signal value and nanoparticles average size were plotted
430 against time of exposure to the pH 4.8 buffer (Figure 5). The obtained values were all normalized by
431 the first one at t_0 .



432

433

Figure 5. Degradation of nanoparticles over time under acidic conditions (pH 4.8 buffer) at various concentrations (top) and size distributions of nanoparticles from t_0 (0% of degradation) to t_{4h} (90% of degradation) with an initial concentration of 0.16g/L (bottom).

434 First, no variation in size measurements meant that DCR measurements were relevant because its
 435 value only depends on the number of nanoparticles in the system. We varied the concentration of
 436 nanoparticles to see if it would change the degradation kinetics. The nanoparticles' average size did
 437 not change drastically with time, whatever the used concentration. In addition, all size distributions
 438 superimpose showing that there is no time evolution of the distribution. From these, we can conclude
 439 that no erosion mechanism occurs, which is in accordance with the fact that nanoparticles are swollen
 440 in water. One can assume that the nanoparticle keeps its integrity until its chains become partially
 441 soluble in water at some critical point, leading to the total solubilization of the nanoparticle. Indeed,

442 no small aggregates resulting from the hydrolysis of the nanoparticle were detected. Kauffmann et
443 al.²² worked on the degradation of microparticles of Ace-dextran and explained that a more or less
444 pronounced burst mechanism could be involved, depending on the ratio of acyclic acetals, which are
445 hydrolyzed first. However, as the pH used for degradation and the particle scale are not the same here,
446 it would not be relevant to directly compare the obtained results.

447 Nanoparticle concentration did have a slight influence on the degradation time (Figure 5 top), but
448 with no clear trend as the 0.04 g/L sample took more time than the 0.08 g/L sample. The shape of this
449 degradation curve is almost linear at the beginning except a small delay for the 0.16 g/L sample. Then
450 the slope starts to decrease to finally reach a plateau (total degradation, limit of detection for DLS).
451 The absence of stirring in the DLC cuvette during the measurements may have influenced the
452 obtained profiles but allowed to follow the degradation in situ and in line.

453

454 Nanoparticle concentration used for the following Pickering emulsions is typically 6 mg/mL oil,
455 corresponding to 1.5 mg/mL water that is almost 10 times more than the highest concentration used
456 in this study (0.16 mg/mL). Making the same experiments at such a high concentration was not
457 possible because of opacity incompatible with DLS measurements.

458

459 **3.4.2. pH-induced destabilization of formulated Pickering emulsions**

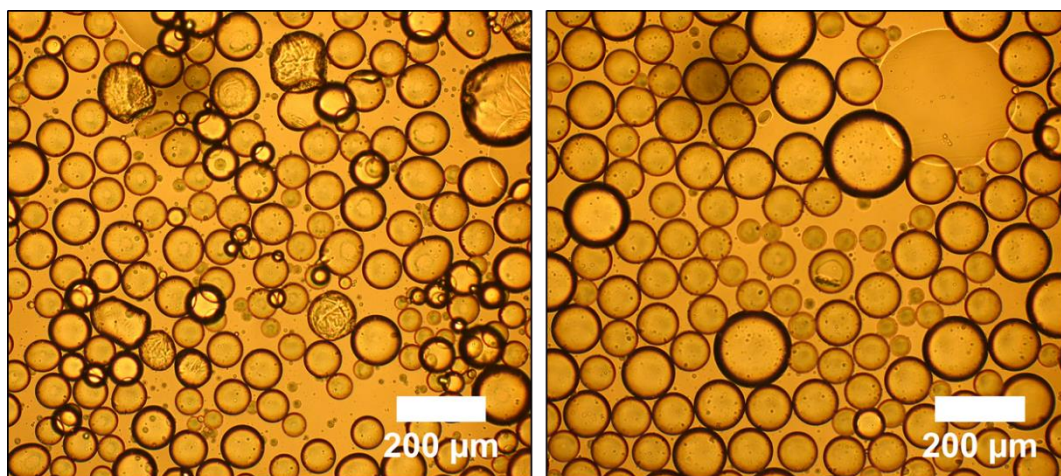
460

461 Formulated Pickering emulsions stabilized by nanoparticles from NPD1 (6 mg / mL of oil) were fully
462 characterized and then subjected to pH-induced destabilization by injection of an acetic buffer at pH
463 4.8. Nanoparticles from this material were hydrolyzed in 6 h according to the previous part, assuming
464 that the high concentration does not impact the degradation kinetics. Thus, emulsions stabilized with
465 such nanoparticles were subjected to destabilization in acidic conditions because of the disappearance
466 of their stabilizers. To better understand the involved mechanisms, both microscopic and macroscopic
467 studies were performed during the destabilization process.

468

469

3.4.2.1. Microscopic study



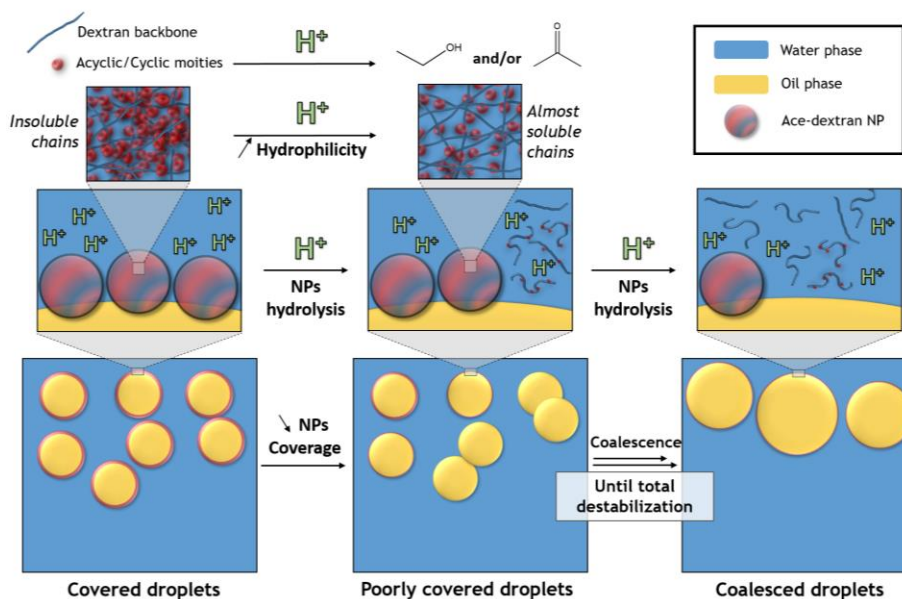
470

Figure 6. Optical microscope images before adding the acidic buffer (left) and 5 h after adding the acidic buffer (right)

471

472 Size measurements performed as shown in Figure 6 showed that the Sauter diameter increased from
473 $75\ \mu\text{m}$ to $110\ \mu\text{m}$ in 5 h. In other words, considering the dispersed phase volume preservation, it
474 corresponds to the coalescence of three droplets on average during this time. Droplets showed only a
475 spherical shape and still a narrow monomodal distribution. From this, we can assume that the
476 coalescence process was quite homogeneous after 5 h. This microscopic effect and the final
477 macroscopic consequence (demixing) are due to a multi-scale succession of events (Figure 7). At the
478 molecular scale, acyclic and cyclic acetals are hydrolyzed continuously into acetone and ethanol
479 because of the aqueous acidic medium. Consequently, at the macromolecular scale the Ace-dextran
480 chains become more and more hydrophilic to a critical point where the whole nanoparticle can be
481 solubilized. Hydrolysis of nanoparticles leads to the decrease in the oil droplets coverage which was
482 rather high at the beginning ($C=0.94$). A coalescence event between two droplets provides an increase
483 in the coverage (26% for initially identically sized drops). To ensure shape relaxation of the new
484 formed droplet, its new coverage should be no more than 0.9. Thus, in the case of two identical
485 droplets, their respective coverage should be at least lower than 0.71. On the other side, coalescence

486 is happening until the coverage of the newly formed droplet is high enough (like the limited
 487 coalescence phenomenon occurring right after formulation). Hence, whereas the degradation of
 488 nanoparticles may be continuous, the emulsion destabilization process is intrinsically discontinuous.
 489 The coverage of a droplet increases right after coalescence but is also continuously decreases because
 490 of the hydrolysis of the nanoparticles, until another coalescence event (Figure 7). In the end, the size
 491 of the droplets becomes too high, leading to macroscopic leakages. Consequently, it is quite certain
 492 that not all the nanoparticles are hydrolyzed neither when the emulsion starts to be unstable nor when
 493 it is totally demixed. However, there is no doubt that they will be all hydrolyzed in the end as they
 494 become more and more available to the water phase that is the same conditions of the pH-induced
 495 degradation of the nanoparticles described earlier (total degradation in 6 h). This scenario is
 496 confirmed by the macroscopic observation.



497 *Figure 7. Multi-scale mechanism for the Pickering emulsion destabilization under acidic pH*
 498 *conditions*

499
 500
 501
 502

3.4.2.2. Macroscopic study

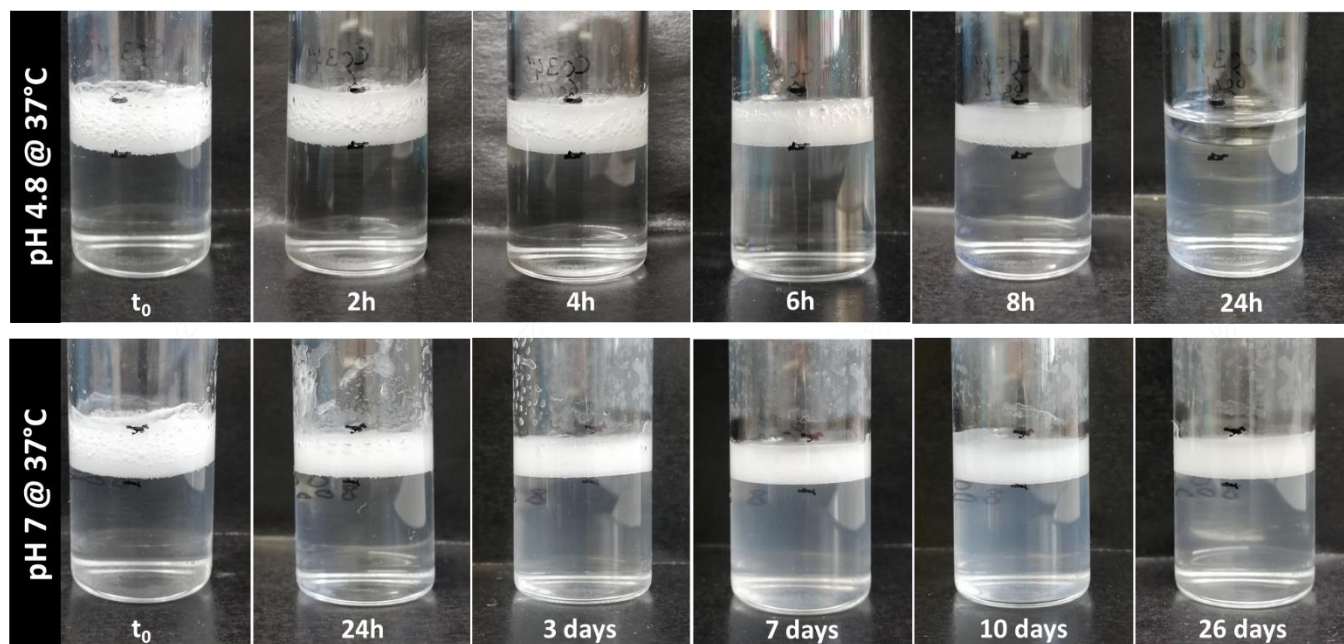


Figure 8. Macroscopic aspects of the formulated emulsions over time – with acidic buffer at pH 4.8 (top) and only with water at pH 7 (bottom) as a control.

Total emulsion destabilization at pH 4.8 after 24 h can clearly be seen on Figure 8. The emulsion cream level did not change a lot, but the cream opacity did attest a size evolution. As the number of droplets (submitted to coalescence as showed before) decreased, it minimized the multiple light scattering which is responsible for the white color of the cream. After 8 h, the emulsion remained stable whereas nanoparticles were fully hydrolyzed after 6 h under the same acidic conditions. This can be due to the lower available surface area when nanoparticles are anchored at the oil/water interface. However, the continuous phase seemed a little bit bluish after 8 h (and 24 h). It means that some nanoparticles were desorbed from the interface, which is in accordance with microscopic observations. The supernatant became completely transparent after few days confirming the total dissolution of the already desorbed nanoparticles. The control sample did not show any major changes over a month, except air bubbles expelling.

519 From this two-scale study, it can be concluded that this Pickering emulsion system is fully demixed
520 in 24 h under acidic conditions and most of all, there is no particle residue in the water medium.

521

522 **3.5. Transferability of the system to other oils**

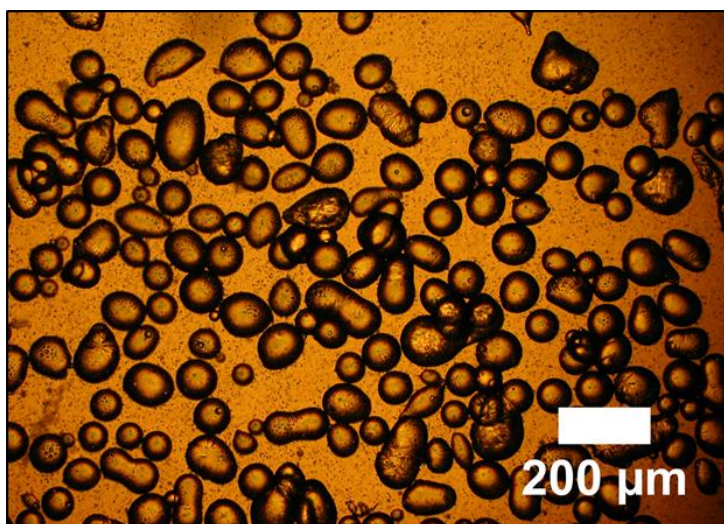
523

524 The adsorption energy of a particle at an oil/water interface is directly proportional to the tension of
525 the oil-water interface. It means that for high values, the energy can be so huge that even a change in
526 affinity would not allow the particle to desorb, this has been observed and explained in a recent
527 published paper dealing also with pH-sensitive Pickering emulsions¹⁴. Thus, we can assume that our
528 system would be easily transferable among a large range of water/oil systems as the destabilization
529 mechanism relies on the degradation of the stabilizer itself and also because tension of the dodecane-
530 water interface is one of the highest ($\gamma = 52.55 \text{ mN.m}^{-1}$ at 25°C ³⁶).

531

532 All the previous studies have been performed using dodecane, a model oil for emulsion science to
533 offer a proof of concept for this new Pickering emulsion system. However, still in the aim of pushing
534 forward efforts for more sustainability, we wished to work with a biocompatible oil extensively used
535 in the field of pharmaceuticals: medium-chain triglyceride (MCT). This kind of oil is much more polar
536 than dodecane and with a higher density (close to the density of water). Nanoparticles from NPD1
537 were used to formulate Pickering emulsions with MCT. The obtained emulsions are of the O/W type
538 (for a 50/50 v/v and for a 80/20 v/v of water and oil).

539



540

Figure 9. Microscopic structure of the MCT-in-water Pickering emulsion with a concentration of nanoparticles of 6 mg/mL of oil

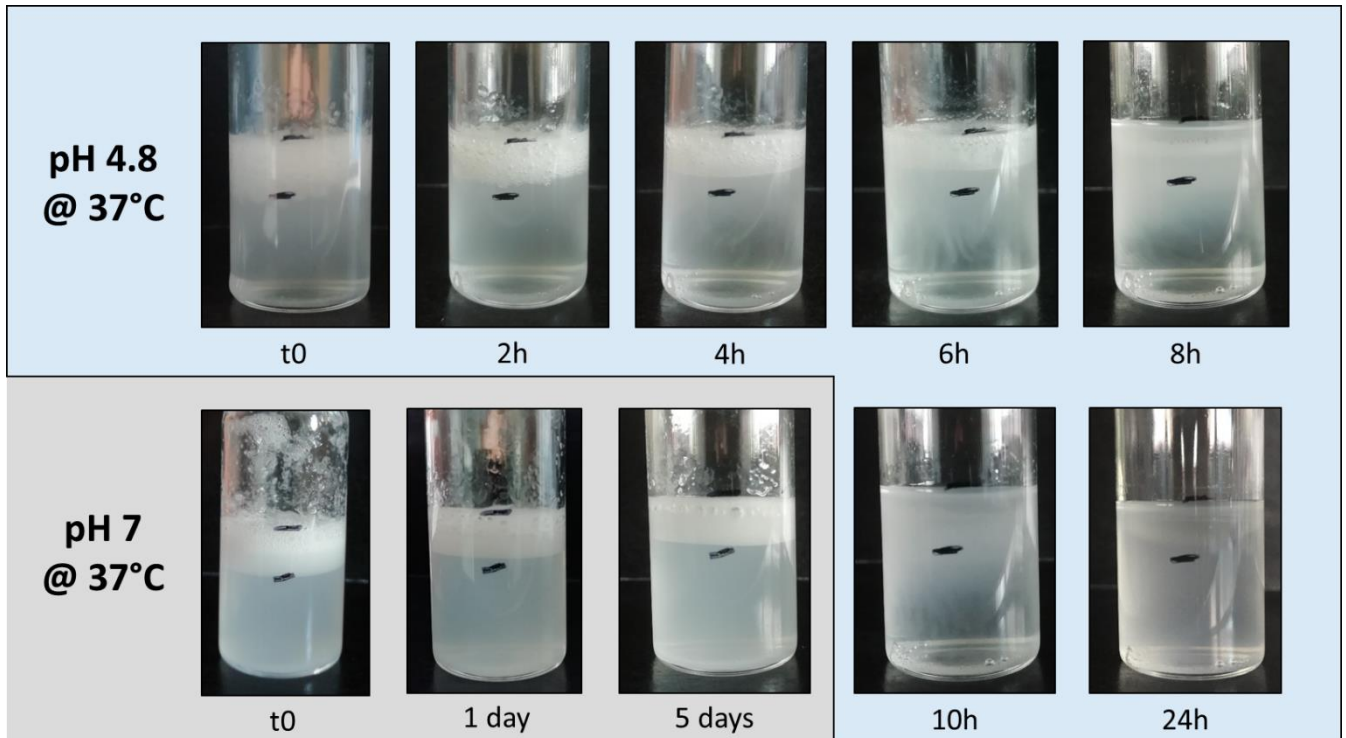
541 Emulsion creaming took more time with MCT emulsions (compared to dodecane emulsions) as their
542 density is closer to the one of water. Shape retention of droplets which started to coalesce can be seen
543 in Figure 9. This phenomenon is typical of Pickering emulsions because interfaces are solid.
544 Dodecane droplets were more spherical, the difference may come from the viscosity difference
545 between the two oils. With a concentration of nanoparticles of 6 mg/mL, the measured $D[3,2]$ was
546 equal to $74 \pm 15 \mu\text{m}$ (more difficult to define because of non-spherical drops). At the same
547 concentration, $D[3,2]$ of dodecane droplets was equal to $90 \pm 19 \mu\text{m}$ which is pretty close.

548

549 Despite their higher polarity, MCT emulsions were kinetically stable over more than 3 weeks at room
550 temperature. It means that both apolar and polar oil droplets could be stabilized by Ace-dextran NPs.
551 Turbid aspect of the subnatants may come from very tiny droplets which did not cream, again because
552 of the higher oil density. However, this population represent an insignificant volume compared to the
553 whole volume of the dispersed phase. Using the same conditions as before, MCT emulsion stabilized
554 by nanoparticles from NPD1 (6 mg / mL oil) was subjected to pH-induced destabilization by injection
555 of an acetic buffer at pH 4.8 (Figure 10). A quicker destabilization (compared to dodecane) seemed

556 to appear 8 h after injection and in less than 24 h, the emulsion is fully demixed. The control sample
557 showed no destabilization clue after 5 days.

558



559

Figure 10: Macroscopic aspects of the MCT emulsions over time – with acidic buffer at pH 4.8 (blue area) and with only water at pH 7 (gray area)

560 This experiment show that the proposed strategy can be generalized. We are therefore convinced that
561 this system will draw attention from both academic and industrial sides because it is fully bio-sourced,
562 biocompatible and biodegradable.

563

564

565

566

567

568 **4. Conclusions**

569 In summary, we modified dextran (a biosourced, biocompatible, and biodegradable polysaccharide)
570 to make it more hydrophobic and pH sensitive. Using nanoprecipitation, we were able to produce for
571 the first time narrow-sized nanoparticles of pure Ace-dextran with a diameter around 200 nm and an
572 average polymer density of 0.685 g/mL determined by MALS. They were then used to formulate
573 stable Pickering emulsions which exhibited the typical limited coalescence phenomenon. This made
574 it possible to produce in a repeatable way, size-controlled and narrow monomodal Pickering
575 emulsions. Nanoparticles of Ace-dextran are degradable under acidic conditions and this hydrolysis
576 yields acetone, ethanol and dextran, three biocompatible and simple (macro)molecules. The Pickering
577 emulsions can be then destabilized by the addition of an acidic buffer, leading to a total system
578 degradation within less than 24 hours. Because Ace-dextran from a 50 min-long synthesis was used,
579 by decreasing (or increasing) this reaction duration one can expect to decrease the time needed to
580 hydrolyze the nanoparticles (or increase respectively)²². This will be of great importance because it
581 means that we can also tune the emulsion degradation time (and for instance the release of active
582 compounds). Pickering emulsions of biocompatible oil MCT were also formulated to obtain a pH-
583 sensitive and totally green system which may be of high interest for biomedical and cosmetics
584 applications. Moreover, catalysis or engineering of original materials³⁷ can be also considered. We
585 are convinced that this new kind of carrier – and a new Pickering emulsion stabilizer class - will
586 attract much interest, as it comprises biomass recovery, tunability and induced degradability.

587

588 **CRedit authorship contribution statement**

589 **V. Maingret:** Conceptualization, Investigation, Writing - original draft. **C. Courrégelongue:**
590 Investigation, Writing - original draft. **V. Schmitt:** Conceptualization, Writing - review & editing,
591 Supervision. **V. Héroguez:** Conceptualization, Writing - review & editing, Supervision.

592

593 Acknowledgments

594 V. M. acknowledges support from the Ministère de l'Enseignement Supérieur, de la Recherche et de
595 l'Innovation for his Ph.D. grant. The authors thank their respective academic institution for financial
596 support. The authors also acknowledge Paul Marque and Christophe Schatz for their help in MALS
597 measurements analysis and Isabelle Ly for Cryo-SEM observations.

599 Supporting information

600 ¹H NMR of Ace-dextran from S1 and S2 and calculations, multi-angle SLS methods calculations and
601 results, DCR calibration curve using NPD2, stacked size distribution curves of NPD1 at t_0 and $t_{10\text{months}}$,
602 and size measurements of Pickering emulsions stabilized by NPD1 nanoparticles.

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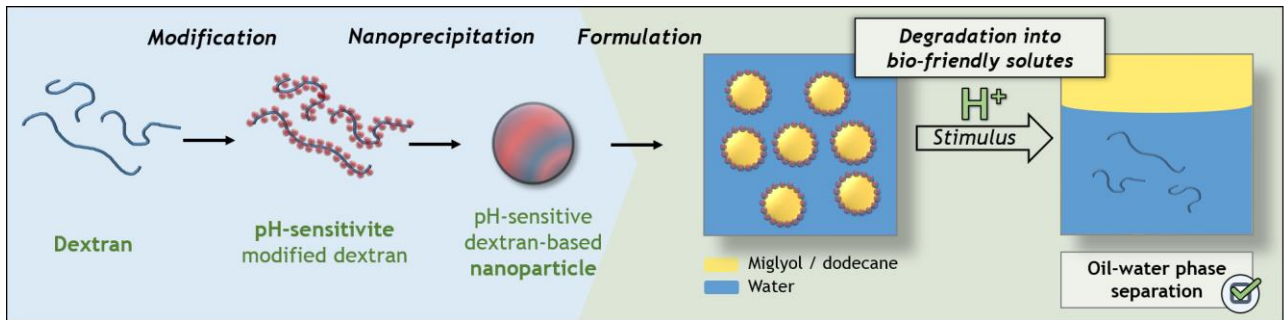
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733 **Table of Contents graphic**

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