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1 **Drug delivery system obtained by hot-melt processing of zein plasticized**
2 **by a pharmaceutically active ionic liquid**

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11
12 **Abstract**

13 Zein-based filaments containing 20 weight% [Lidocainium][Ibuprofenate] used as a doubly
14 Active Pharmaceutical Ingredient - Ionic Liquid (API-IL) were obtained by extrusion at 130°C.
15 The plasticizing effect of the active ingredient on the zein amorphous matrix was assessed by
16 Differential Scanning Calorimetry, with the decrease of the glass transition temperature (T_g)
17 from 77°C, for the raw zein, to 53°C. After storage under standard conditions (relative humidity
18 59%, 20°C) the extrudates were rigid, with a high storage modulus (E') at ambient temperature
19 of about 3 GPa. They had a main mechanical relaxation (T_α) beginning at 55°C and leading to
20 their flowing at temperature above 130°C, as determined by Dynamic Mechanical Analysis,
21 with E' below 1 MPa and $\tan\delta$ above 1. Their structure was evaluated by Wide Angle X-ray
22 Scattering and NMR analyses were used to evaluate the API-IL stability that was shown after
23 thermomechanical processing. Release experiments performed under simulated physiological
24 conditions on filaments evidenced a release of 85% after 7 days immersion. These results
25 demonstrate the interest of using an API-IL to act as plasticizer for a resorbable biopolymer.

26 The resulting material can be shaped by continuous thermomechanical process and used as drug
27 delivery system.

28

29 **1. Introduction**

30 Biopolymers are of increasing interest to obtain edible and resorbable matrices in the
31 pharmaceutical and biomedical fields. The potential of zein, the main storage protein in corn
32 kernels, has been investigated in recent years for this kind of applications¹, especially for the
33 controlled release of pharmaceutically active ingredients (PAM).^{2,3} This prolamin has an amino
34 acids sequence which is rich in apolar residues (> 50 mol%), giving hydrophobic properties,
35 but interactions with polar chemical compounds are also possible, especially because of polar
36 glutamine residues (\approx 30 mol%). Thermoplastic properties of zein led to its hot-melt processing
37 as cylindrical caplets, which have been shown to present tuneable release rates depending on
38 their shape factor (*i.e.*, the length/diameter ratio) in the case of an uncharged crystalline drug as
39 paracetamol.⁴ Water solubility, as well as electrostatic interactions between charged drugs and
40 the thermoplastic zein-based matrix were also shown to impact the release in phosphate buffers
41 of hydrophobic PAM, such as indomethacin with a low release rate, and hydrophilic ones, such
42 as ranitidine, presenting a fast release.⁵

43 Active Pharmaceutical Ingredient - Ionic Liquids (API-IL) are considered as among the most
44 promising compounds for future drugs, especially because they can be easily dosed and
45 processed to prepare pharmaceuticals with better solubility, absorbability and stability than
46 solid forms.⁶ The release of API-IL from edible and resorbable matrices is the next step of using
47 these drugs^{7, 8}, as in the case of protein-based materials because of numerous potential
48 interactions between such hetero-polymers and active ingredient molecules^{8, 9} and recently
49 highlighted especially for zein.^{10, 11} [Lidocainium][Ibuprofenate], named [Lid][Ibu], has a triple
50 interest : (i) a plasticizing effect on biopolymers (*e.g.* PLA-[Lid][Ibu]¹²) and two therapeutic

51 roles due to its constitutive molecules¹³, with (ii) the cation (Lidocainium) as a local
52 anaesthetic¹⁴ and (iii) the anion (Ibuprofenate) as nonsteroidal anti-inflammatory compound.¹⁵

53 ¹⁶

54 The blending of Ibuprofen itself (as a non-ionic molecule) with zein has been previously
55 described in literature, allowing its progressive release from electrosprayed microparticles.¹⁷

56 In addition, the extrusion of zein with ionic liquids (23% w/w) used as plasticizers was also
57 reported.^{18, 19} However, these works mainly focused on tensile mechanical properties at 25°C

58 of a such amphiphilic matrix.²⁰ The use of a commercial imidazolium ionic liquid (1-butyl-
59 3-methyl imidazolium chloride: [BMIM][Cl]) leads to plasticized zein with rubber like
60 behaviour (Elastic modulus < 10 MPa and Elongation at break > 400%).^{18, 19} Concurrently,

61 plasticization with a synthesized cholinium acetate ionic liquid leads to more rigid and brittle
62 behaviour (Elastic modulus > 180 MPa and Elongation at break < 10%).¹⁹

63 In the present work, we describe the extrusion of zein plasticized by 20w%
64 [Lidocainium][Ibuprofenate] ([Lid][Ibu]), as an alternative process to conventional galenics,
65 such as powder compression or soluble capsules gelation, for obtaining drug delivery systems.

66 The objective is to take advantage of expected plasticizing effect of the pharmaceutically active
67 ionic liquid to hot melt process zein by extrusion, in order to obtain calibrated parts containing
68 a high degree of ingredients mixing.

69 The thermoplastic material obtained was fully characterized : the thermal properties were
70 determined by means of thermogravimetric analysis (TGA), differential scanning calorimetry
71 (DSC) and dynamic mechanical thermal analysis (DMTA). Wide Angle X-ray Scattering
72 (WAXS) was used to investigate the molecular structure and liquid-state and solid-state NMR
73 to study the API-IL stability and its dynamic. Finally, both the evolution of the mechanical
74 properties of the extruded filaments and the release kinetics of the doubly-active ionic liquid
75 drug in PBS media were investigated by immersion in PBS at 37°C. This allows evaluating the

76 affinity between the [Lid][Ibu] PAM and the zein matrix, as well as the potential of the blend
77 to constitute a slow drug delivery system.

78

79 **2. Experimental section**

80 **2.1. Raw materials**

81 Zein in the powdery state (Ref. Z3625, containing 5% moisture) was purchased from Sigma-
82 Aldrich (Saint-Quentin-Fallavier, France). Chemicals were purchased and used as received : 4-
83 isobutyl- α -methylphenylacetic acid 99 % (Ibuprofenic acid) from Alfa Aesar (Haverhill, MA,
84 US), Lidocaine from Sigma-Aldrich and phosphate buffered saline (PBS) tablets from Fisher
85 Chemical (Fisher Scientific SAS ; Illkirch, France). The ionic liquid drug [Lid][Ibu], was
86 prepared according to the procedure reported in our previous work.¹²

87 **2.2. Powder blend, extrusion and storage of the extrudates**

88 Prior to extrusion, 20 weight% [Lid][Ibu] was added to zein based on the weight of the raw
89 commercial zein, and mixed in a household kneader (De'longhi Kenwood ; Clichy, France) for
90 2 min at 20°C. This powder mixture, named Z20[Lid][Ibu]_{pow}, was processed with a twin-screw
91 microcompounder (Haake Minilab, Thermo Scientific GmbH ; Karlsruhe, DE) set at 50 rpm
92 and extruded without recirculation through a cylindrical die ($\varnothing_{\text{die}} = 2$ mm) to obtain a brief
93 thermomechanical treatment, typically about 1 minute at 130°C.

94 The extruded filaments, named Z20[Lid][Ibu]_{fil}, were stored at a stable intermediate relative
95 humidity of 59% during one week at 20°C, before subsequent DMTA, WAXS, NMR and *in*
96 *vitro* release characterizations. They were cryoground in liquid nitrogen as fine particles and
97 then stored under the same stable conditions (RH=59%, 20°C, 1 week), to fill the airtight cells
98 for DSC and the crucibles for TGA.

99 **2.3. Characterizations**

100 **2.3.1. Thermogravimetric Analysis (TGA)**

101 About 10 mg samples were placed in a ceramic crucible and weighted while submitted to
102 heating at 10 °C/min up to 500°C, under nitrogen flow (Model TGA-2050, TA Instruments -
103 Waters SAS ; Guyancourt, France).

104 2.3.2. *Dynamic Mechanical Thermal Analysis (DMTA)*

105 On dry samples, the dynamic mechanical analyses were performed on extruded filaments
106 ($\text{Ø}_{\text{filament}} \approx 2 \text{ mm}$; $L_{\text{filament}} = 15 \text{ mm}$) with a Dynamic Mechanical Thermal Analyser (DMTA,
107 model MK-IVA, Rheometric Scientific Inc. ; Piscataway, NJ -US-). Prior to DMTA trials,
108 filaments were coated with a silicone-based hydrophobic grease to limit their dehydration. The
109 length between the two grips was set to 5 mm and specimens were characterized in the tensile
110 mode at a frequency (ν) of 1 Hz, with a strain (ϵ) set at 0.01% and heating rate at 3 °C.min⁻¹
111 from -50 to 140 °C.

112 Under simulated physiological conditions, filaments were submitted to a mechanical
113 characterization while immersed in PBS at 37°C (pH = 7.5). It has been carried out with the
114 same DMTA device as on dry extrudates, but reversed to immerse the sample maintained by
115 the clamps of the load cell in a 300 mL glass tempering beaker full of phosphate buffered saline.
116 The mechanical active length between the two grips was set at 5 mm and the beaker was
117 thermostated at 37°C thanks to the flow of water between its two surrounding glass walls. The
118 cylindrical filaments were characterized in the tensile mode during 96 h immersion, with $\epsilon =$
119 0.01% initially, 0.1% after 2 h immersion and 0.5% for immersion time longer than 12 h, to
120 obtain a static force above 5mN (minimum measurable force for the DMTA).

121 2.3.3. *Differential scanning calorimetry (DSC)*

122 Thermal transitions were determined with an automated differential scanning calorimeter DSC
123 (Model Q100, TA Instruments ; Guyancourt, France). The specimen ($\approx 10 \text{ mg}$) was placed in a
124 sealed aluminium cell. Measurements were carried out at 3 °C.min⁻¹ from -50 to 140 °C during

125 a second scan so as to delete any thermal event due to aging during storage. The glass transition
126 temperature, T_g , is detected at the midpoint of the calorific capacity change on the thermogram.

127 *2.3.4. Wide Angle X-ray Scattering (WAXS)*

128 Diffractograms were recorded during 10 min using an X-ray diffractometer (Bruker AXS,
129 device model D-8 ; Fitchburg, MA -US-). The X-ray radiation $\text{Cu-K}\alpha_1$ ($\lambda=1.5405 \text{ \AA}$) produced
130 at 40 kV and 40 mA was selected, parallelized and collimated to produce a 500 μm beam
131 diameter.

132 *2.3.5. Solid state NMR (CP-MAS and DP-MAS)*

133 The NMR experiments were carried out on a AvanceIII-400 MHz spectrometer (Bruker;
134 Champs-sur-Marne, France) operating at 100.58 MHz for ^{13}C , equipped with a double-
135 resonance H/X CP-MAS 4-mm probe for CP-MAS (Cross-Polarization Magic Angle Spinning)
136 and DP-MAS (Direct Polarization Magic Angle Spinning) solid-state experiments. The samples
137 were spun at 9000 Hz at room temperature.

138 CP-MAS spectra were acquired with a contact time of 1.5 ms and over accumulation of 5120
139 scans separate of 10 s as recycling delay.

140 DP-MAS spectra were acquired with a ^{13}C 90° pulse of 4 μs and over accumulation of 10240
141 scans separate of 5 s as recycling delay. The carbonyl carbon was set to 176.03 ppm through
142 external glycine calibration.

143 *2.3.6. Liquid state NMR*

144 ^1H and ^{13}C liquid-state NMR spectra were obtained on a Bruker Avance III-400 MHz
145 spectrometer (Bruker; Champs-sur-Marne, France). Chemical shifts (δ) are given in ppm and
146 are referenced to residual solvent peaks (DMSO-d_6 : δ 2.50 ppm ^1H and δ 39.52 ppm ^{13}C).

147 *2.3.7. In vitro release*

148 Experiments were performed by dipping the samples into 300 mL of PBS (pH = 7.5) maintained
149 at 37°C under constant stirring at 50 rpm. Aliquots of 2 mL were taken for UV analysis and

150 replaced by fresh PBS medium. All experiments were performed in duplicate. The amount of
151 drug released was evaluated by UV spectroscopy at 225 nm on a Varian CARY 3 UV-visible
152 spectrophotometer (Agilent, CA -US-). For this, a calibration curve was first obtained using
153 different PBS solutions of [Lid][Ibu] with known concentrations and measuring their
154 absorbance at 225 nm (please see the Supplementary Data #1 section, Fig.SD-1).

155

156 **3. Results and discussion**

157 **3.1. Thermal stability**

158 Thermogravimetric analyses of the powdery zein, the neat ionic liquid [Lid][Ibu] and their
159 blends, Z20[Lid][Ibu]_{pow} and Z20[Lid][Ibu]_{fil} lead to the evaluation of their moisture content
160 considering the weight loss up to 100°C. It is about 5w% of the total wet basis for the raw
161 protein, 3w% for the powder blend Z20[Lid][Ibu]_{pow} and 4w% for the filament Z20[Lid][Ibu]_{fil},
162 while no weight loss is measured for the sole [Lid][Ibu] being dry after synthesis and stored in
163 a closed vial (Fig.1). The thermal stability of Lidocaine and Ibuprofen has been previously
164 reported up to 150°C in the literature.^{14, 15} In the present case, no significant weight loss is found
165 in the same temperature domain for the IL [Lid][Ibu]. Zein presents a main thermal
166 decomposition above 250°C, with a slight progressive thermal degradation at temperature
167 above 180°C. In the sole zein, its blend with [Lid][Ibu] and after extrusion, two thermal steps
168 are clearly visible after the loss of water. The first one, from 150 to 250°C, corresponds to the
169 decomposition of [Lid][Ibu] and occurs at slightly higher temperature than for the sole IL.
170 Various but efficient protective interactions (*e.g.*, hydrogen bonds, hydrophobic and
171 electrostatic interactions), have been shown to enhance the thermal stability of ionic liquid -
172 protein blends.⁹ The second one from 250 to 500°C is ascribed to the decomposition of zein
173 and is lightly shifted to lower temperature after incorporation of [Lid][Ibu]. From these results,
174 it can be concluded that a thermomechanical treatment is possible up to about 150°C. After

175 thermal treatment, the TGA trace of the filament Z20[Lid][Ibu]_{fil} looks rather similar to the one
176 obtained on the powder form, but the onset of the zein decomposition is slightly shifted to lower
177 temperature.

178 **3.2. Filaments processing and thermomechanical properties**

179 The extrusion is carried out at 130°C with the microcompounder to obtain filaments,
180 Z20[Lid][Ibu]_{fil}, as straight cylinders ($\varnothing_{\text{filament}} \approx 2\text{mm}$), with an average specific mechanical
181 energy (SME) measured at about 40 J.g⁻¹ during processing (please see the Supplementary Data
182 #2 section). The filaments appear as stable monoliths after extrusion, without phase separation.
183 They are rigid at ambient conditions, after storage at stable relative humidity of 59 % during
184 one week, with a storage modulus E' measured by DMTA at about 3 GPa at 20°C (Fig.2-a).
185 They present a main mechanical relaxation which onset, T_{α_onset}, is found at about 55°C.

186 Comparatively, the previously reported plasticization of zein by a [BMIM][Cl] commercial
187 ionic liquid had shown much lower values of E' at 20°C (≈ 0.2 GPa) due to a mechanical
188 relaxation starting at lower temperature (T_{α_onset} ≈ -10°C).¹⁸ Despite the glass transition
189 temperature T_g was not measured in this earlier work, this suggests that [BMIM][Cl] should be
190 a more efficient glass transition temperature depressor than [Lid][Ibu]. For this later point, the
191 glass transition results in a drop of the heat flow measured by DSC from 10 to 70°C (Fig.2-b).
192 In this broad range, the midpoint glass transition temperature is estimated at 53°C. This glass
193 temperature of the blend is in between those of the pristine two components : Pure [Lid][Ibu]
194 shows a glass transition at -30°C, while the one of the raw zein is found at 77°C (Fig.2-b). This
195 suggests that their blend is miscible. The application of the Fox law supports this assumption²¹

196 :

$$197 \frac{1}{T_{g_blend}} = \frac{17/100}{T_{g_Lid}[Ibu]} + \frac{83/100}{T_{g_zein}} \quad (\text{Eq. 1})$$

198 This leads to a theoretical value of the glass transition temperature of the blend, T_{g_blend}, at about
199 52°C, which is very close to the measured one at 51-53°C. Moreover, the DMTA results

200 confirm the presence of a single mechanical relaxation associated to the glass transition of the
201 extruded blend. On the figure 2-b, the thermogram obtained for the powder state blend,
202 Z20[Lid][Ibu]_{Pow}, before extrusion is also plotted. A very broad transition is also observed in
203 the same temperature range, from 10 to 70°C, with a midpoint glass transition about 51°C. This
204 suggests that miscibility already starts to be obtained before extrusion.

205 The extruded material Z20[Lid][Ibu]_{Fil} is in the vitreous state at 20°C. This leads to
206 mechanically stable cylindrical parts, with a constant shape when stored at standard
207 temperature, before their potential subsequent end-use as pharmaceutically active materials. At
208 temperature above their mechanical relaxation, typically $T > 130^{\circ}\text{C}$, the extrudates have a very
209 weak modulus, with E' below 1 MPa and damping factor above 1. They flow and may expand
210 between the grips of the DMTA, leading to a jagged signal at the highest temperatures (Fig.2-
211 a).

212 The mechanical relaxation associated to the glass transition occurs on a broad temperature
213 range, in agreement with the DSC thermograms. The loss angle curve shows a main peak at a
214 temperature about 100°C, with a small shoulder at about 75°C. These observations may be
215 ascribed to an inhomogeneous distribution of the API-IL in the extruded zein matrix which
216 remains macroscopically stable without exudation of [Lid][Ibu], even after being stored for
217 several months. The absence of any secondary thermomechanical event at low temperatures
218 down to the glass transition of the sole plasticizer ($T_{g_}[\text{Lid}][\text{Ibu}] = -30^{\circ}\text{C}$), as assessed by DMTA
219 and DSC during the characterization of the extruded specimen, Z20[Lid][Ibu]_{Fil} confirms the
220 absence of phase separation between zein and [Lid][Ibu].

221 ***3.3 Structural characterization***

222 The structure of zein samples plasticized with 20% [Lid][Ibu] before (Z20[Lid][Ibu]_{Pow}) and
223 after extrusion (Z20[Lid][Ibu]_{Fil}) was analysed by WAXS and compared to the diffractograms
224 obtained with the sole zein (Fig.3). X-ray diffractograms present two broad amorphous

225 scattering bands centred at 4.5 and 9.5 Å, typical of α -helices backbone and packing,
226 respectively.²²⁻²⁴ As such, the presence of the ionic liquid does not modify such level of
227 organisation of the protein in the powder blend with zein and after its thermomechanical
228 treatment by extrusion. Furthermore, no characteristic peaks of crystalline Ibuprofen or
229 Lidocaine were observed.

230 The molecular structure of the IL in the extruded Z20[Lid][Ibu]_{Fil} sample was assessed by
231 recording both ¹H and ¹³C NMR spectra after dissolution in deuterated DMSO and was
232 compared to the spectra of raw zein and [Lid][Ibu] recorded in the same conditions (please see
233 the Supplementary Data #3 section). As shown in figures SD-3-a and SD-3-b, all the peaks
234 attributable to both raw zein and [Lid][Ibu] are clearly present in the spectra of extruded
235 Z20[Lid][Ibu]_{Fil} meaning that the IL was not degraded during processing.

236 ***3.4. Ionic liquid mobility***

237 The molecular mobility of [Lid][Ibu] into zein obtained as powder blend or as an extruded
238 filament was study by ¹H and ¹³C solid state NMR. Figure 4-a compares the ¹H MAS NMR
239 spectra of samples Z20[Lid][Ibu], before (Z20[Lid][Ibu]_{Pow}) and after extrusion
240 (Z20[Lid][Ibu]_{Fil}), with those of raw zein obtained in the solid state and sole [Lid][Ibu] recorded
241 in the liquid state. ¹H-MAS spectra of the two Z20[Lid][Ibu] samples present characteristics
242 peaks of zein between 0.2 and 2.5 ppm. However, some differences are also noticeable. The
243 spectrum obtained for the powder form presents also signals attributable to the aromatic
244 hydrogens of [Lid][Ibu] that are clearly visible in the region 6.2-7.2 ppm.¹² The intensity of
245 these peaks is much lower for the filament and, moreover, a signal at about 5.0 ppm due to the
246 hydrogens of the unsaturated aliphatic carbons from fatty acids of zein is observed.²⁵

247 The ¹³C DP-MAS NMR spectrum of the sample in the filament form presents signals at 10 to
248 70 ppm attributable to amino acid aliphatic chain and α carbons, while the broad signal at 170-
249 180 ppm is attributed to carbons of the carbonyl groups of zein²⁶ (Fig.4-b). In the ¹³C MAS

250 spectrum of the powder form, additional signals attributable to the API-IL are clearly observed
251 in the 120-140 ppm region corresponding to aromatic carbons. The presence in both ^1H and ^{13}C
252 NMR spectra of peaks attributable to the API-IL in the case of the powder mixture
253 Z20[Lid][Ibu]_{Pow} clearly indicates a higher mobility of the API-IL before extrusion.

254 By solid-state ^{13}C NMR characterization, the mobility of samples is further investigated at the
255 nanometric scale and can be compared (please see the Supplementary Data #4 section). The
256 highly rigid part is shown with the CP-MAS sequence (Fig.SD-4-a), while the more mobile part
257 is evidenced with the DP-MAS sequence (Fig.SD-4-b). The powder blend, Z20[Lid][Ibu]_{Pow},
258 has the same peaks intensity in the CP-MAS spectrum as the one of the raw zein for the rigid
259 part (Fig.SD-4-a), suggesting that the ionic liquid drug [Lid][Ibu] is relatively mobile, as
260 complementarily depicted with narrow peaks corresponding to [Lid][Ibu] in DP-MAS (Fig.SD-
261 4-b).

262 In the case of the extruded sample, Z20[Lid][Ibu]_{Fil}, the signal between 100 and 150 ppm on
263 the CP-MAS spectrum is significantly increased (Fig.SD-4-a), jointly with a decrease of the
264 narrow peaks on the DP-MAS spectrum (Fig.SD-4-b). These data clearly show that the mobility
265 of [Lid][Ibu] is significantly decreased after being thermomechanically processed by extrusion.
266 This important change in mobility can be ascribed to an increase of the intensity of the
267 interactions between the zein matrix and the ionic liquid drug after extrusion. While DSC results
268 suggested that miscibility was already started to be obtained in the powder mix, these NMR
269 results point out the importance of the extrusion process for the dispersion of the miscible drug
270 at molecular level.

271 ***3.5. Mechanical properties and release abilities in simulated physiological conditions***

272 To evaluate the potential of the zein-based extruded material to be a drug delivery matrix, once
273 plasticized by [Lid][Ibu], an extruded filament Z20[Lid][Ibu]_{Fil} is immersed in PBS at 37°C.
274 The evolution of its mechanical properties is fast during the first hours. Its storage modulus

275 decreases briefly from a high rigidity, with E' about 2.5 GPa for the dry sample under ambient
276 conditions, to about 50 MPa after 1 hour immersion in PBS at 37 °C, 5 MPa after 2 hours and
277 0.1 MPa after 24 hours. The water uptake from the surrounding medium leads to a change in
278 the material from a vitreous to a rubbery state during the three first hours of immersion, with a
279 fast decrease of E' below 1 MPa (Fig.5). Then, it is nearly stable with only a slight increase of
280 the storage modulus reaching 0.5 MPa after about 96 hours immersion. The superimposed
281 following of the [Lid][Ibu] release, from a piece of the same filament, shows that about 65% of
282 its initial amount is freed during such an immersion time (Fig.5, right axes). The loss of the
283 ionic liquid, diffusing in the surrounding medium and presenting a plasticizing effect on the
284 zein-based matrix, may be at the root of this progressive slight stiffening after an important
285 softening step during the firsts 24 hours. The cylindrical shape is maintained during about 4
286 days in PBS at 37 °C and then the sample slips between the clamps of the DMTA, limiting the
287 measurement of its mechanical properties beyond this duration.

288 The release of the API-IL in similar conditions, followed up by spectrophotometry, presents a
289 progressive loss from the filament, $Z20[\text{Lid}][\text{Ibu}]_{\text{fil}}$, whereas it is a quasi-instantaneous release
290 from the powder blend $Z20[\text{Lid}][\text{Ibu}]_{\text{pow}}$ (Fig.6).

291 In the latter case, 90 % is released in 15 min (Fig.6-a), whereas it takes more than one week
292 from filaments based on the same composition (Fig.5 and Fig.6-b). The fastest release observed
293 for $Z20[\text{Lid}][\text{Ibu}]_{\text{pow}}$ in such a powder form is in accordance with the higher mobility of the IL
294 observed by solid-state NMR (*vide supra*).

295 Concerning the filament, a Fickian diffusion is obtained, with the n exponent about 0.5 in the
296 following power law, adjusted to the release kinetics of [Lid][Ibu] from filaments :

$$297 \frac{M_t}{M_0} = K \cdot t^n \quad (\text{Eq. 2})$$

298 with M_t [mg], the amount of [Lid][Ibu] released at instant t ; M_0 , the initial amount of [Lid][Ibu]
299 [mg] (about 10 to 15mg for filaments weighting 50 to 70 mg after cutting about 15 mm long);

300 K , the kinetics constant characteristic of the polymeric matrix and the diffusing species and n ,
301 the exponent indicating the transport mechanism, with $n = 0.5$ for a Fickian diffusion.²⁷
302 Such a progressive release of the active ingredient should be particularly of interest to target
303 pharmaceutical, or biomedical, applications for these filaments, especially for a delayed
304 delivery of the drug, when compared to a fast release in the case of the simple powder blend.
305 Release rates can be compared with those obtained for the same ionic liquid in different solid
306 matrices. Bica and co-workers immobilized the same API-IL into mesoporous silica matrices
307 and obtained a total release within a few minutes in PBS media.¹⁵ In this case, low interactions
308 between [Lid][Ibu] and the silica matrices favour its fast release as in the case of our
309 Z20[Lid][Ibu]_{Pow} sample. In the presence of higher interactions between [Lid][Ibu] and the solid
310 matrix, as in the case of PLLA, slower releases occurring within couple of hours or more than
311 15 days were obtained.¹² Our release rates are thus also dependent to IL/matrix interactions that
312 are reinforced by thermomechanical processing in the present case.
313 Concerning the release of [Lid][Ibu] from the zein-based filaments (Z20[Lid][Ibu]_{Fil}), the
314 Peppas model was applied to determine the diffusion coefficient D [m²/s], in the case of
315 transport model for a cylindrical geometry.²⁷ This shape was checked as being maintained
316 during 4 days immersion in PBS at 37°C during inversed DMTA trials on immersed specimen,
317 corresponding to about 60 % [Lid][Ibu] release (Fig.5 and Fig.6-b). This is in the application
318 range of the Peppas model and the solution of the Fick's law is presented in the following
319 relationship :

$$320 \quad \frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{4}{a^2 \cdot \alpha_n^2} \cdot \exp(-D \cdot \alpha_n^2 \cdot t) \quad (\text{Eq. 3})$$

321 with α_n , the positive roots of $J_0(a \cdot \alpha_n) = 0$; J_0 , the Bessel function of the first kind of order
322 $a \cdot \alpha_n$ the zeros of this function.

323 The diffusion coefficient is computed at $D = 2.9 \cdot 10^{-13}$ m².s⁻¹, with $M_t/M_0 = 0.57$, after 72h
324 immersion of filaments in PBS at 37°C. This value is less important than a hot melt processed

325 material based on zein with 22% paracetamol added as active ingredient, with D about 3.10^{-12}
326 to $5.10^{-12} \text{ m}^2.\text{s}^{-1}$.⁴

327 The tenfold decrease of the diffusion coefficient in the case of the ionic liquid form of Ibuprofen
328 may be ascribed to a higher affinity of the [Lid][Ibu] ion pair with the zein extruded matrix.
329 This assumption is supported by the DSC and NMR results, indicating that the blend is miscible
330 and that strong interactions are present between zein and the ionic liquid dispersed at molecular
331 level. Such links are needed to form biopolymer-IL supramolecular complexes in a more stable
332 way than in the case of ionogels, or films, to deliver active compounds.^{7, 10}

333

334 **4. Conclusion**

335 The pharmaceutically-active ionic liquid [Lidocainium][Ibuprofenate] acts as a plasticizing
336 agent on zein rendering processable the thermoplastic blend as a hot melt by a
337 thermomechanical treatment such as extrusion at 130 °C, to shape this material as filaments.
338 From such parts, a progressive release of the active ingredient is obtained in simulated
339 physiological conditions, with 85% freed after one week immersion. Thus, an important affinity
340 has been highlighted between the zein-based matrix and [Lidocainium][Ibuprofenate], leading
341 to a pertinent material to target applications in pharmaceutical or biomedical fields. It is
342 especially the case to reach a progressive release of such pharmaceutically active ingredient,
343 thanks to molecular blend and strong interactions favoured by extrusion process as shown in
344 the present study. Moreover, plasticized zein can be processed by additive manufacturing,
345 leading to pharmaceuticals with targeted porous structures and potentially presenting customized
346 drug release kinetics. A blend including plasticized zein and [Lidocainium][Ibuprofenate] may
347 be interesting for such thermomechanical processing and extended in the future to other ionic
348 liquid-containing drugs.

349

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352 helpful discussions and experimental support.

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398 **Figure captions**

399 **Figure 1.** Thermogravimetric analysis carried out on the raw zein, the pure ionic liquid
400 [Lid][Ibu], their powder blend Z20[Lid][Ibu]_{Pow} and extruded as filament Z20[Lid][Ibu]_{Fil}.

401
402 **Figure 2.** Dynamic mechanical properties determined on the extruded Z20[Lid][Ibu]_{Fil} (a-) and
403 DSC thermograms acquired on the pure IL [Lid][Ibu] (with $T_{g_Lid}[Ibu] = -30^{\circ}\text{C}$), the raw zein
404 ($T_{g_Zein} = 77^{\circ}\text{C}$), their powder blend Z20[Lid][Ibu]_{Pow} ($T_{g_Z20[Lid][Ibu]Pow} = 51^{\circ}\text{C}$) and after
405 extrusion Z20[Lid][Ibu]_{Fil} ($T_{g_Z20[Lid][Ibu]Fil} = 53^{\circ}\text{C}$) (b-).

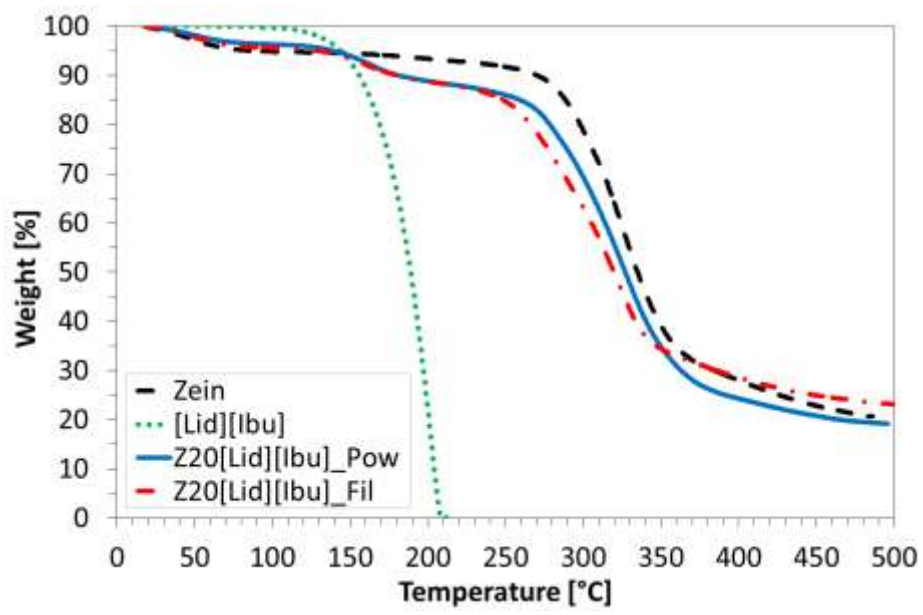
406
407 **Figure 3.** WAXS diffractograms obtained on the raw zein, the powder blend Z20[Lid][Ibu]_{Pow}
408 and after extrusion Z20[Lid][Ibu]_{Fil}.

409
410 **Figure 4.** ^1H MAS NMR spectra of extruded filament (Z20[Lid][Ibu]_{Fil}), powder blend
411 (Z20[Lid][Ibu]_{Pow}), raw zein and ^1H NMR of pure [Lid][Ibu] in DMSO- d_6 (a-). ^{13}C DPMAS
412 NMR spectra of extruded filament (Z20[Lid][Ibu]_{Fil}), powder blend (Z20[Lid][Ibu]_{Pow}), raw
413 zein and ^{13}C NMR of pure [Lid][Ibu] in DMSO- d_6 (b-).

414
415 **Figure 5.** Dynamic mechanical properties of extruded Z20[Lid][Ibu]_{Fil} immersed in PBS at
416 37°C and release of [Lid][Ibu] in similar conditions from such extruded filament. Photographs
417 of the sample during its immersion (maintained between the clamps of the DMTA) and out the
418 buffer at the end of the experimental testing (4 days immersion).

419
420 **Figure 6.** Release of [Lid][Ibu] followed-up in PBS at 37°C during the immersion of
421 Z20[Lid][Ibu] as a powder blend (Z20[Lid][Ibu]_{Pow} ; a-) and as an extruded filament
422 (Z20[Lid][Ibu]_{Fil} ; b-).

423

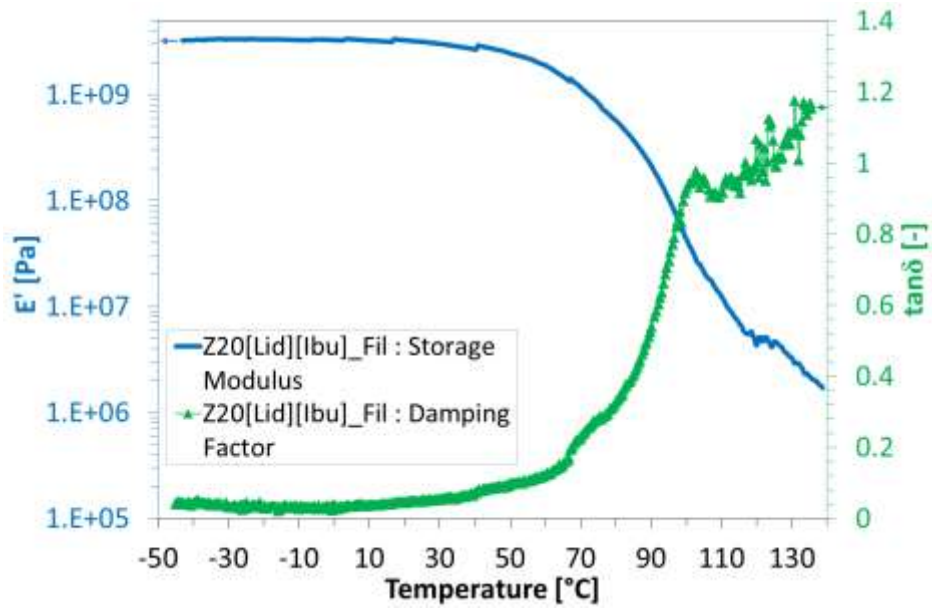


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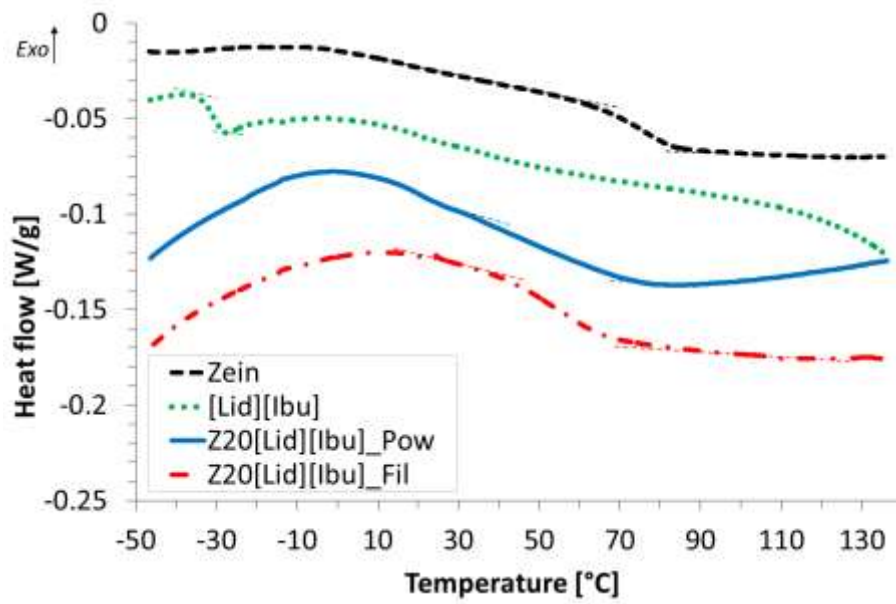
425 **Figure 1.** Chaunier *et al.*

426

a-



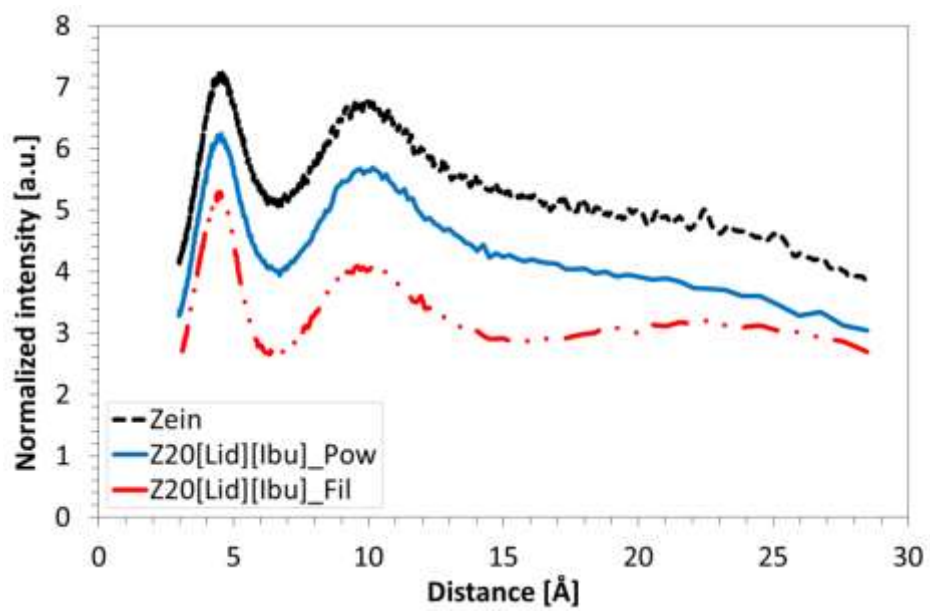
b-



427

428 **Figure 2.** Chaunier *et al.*

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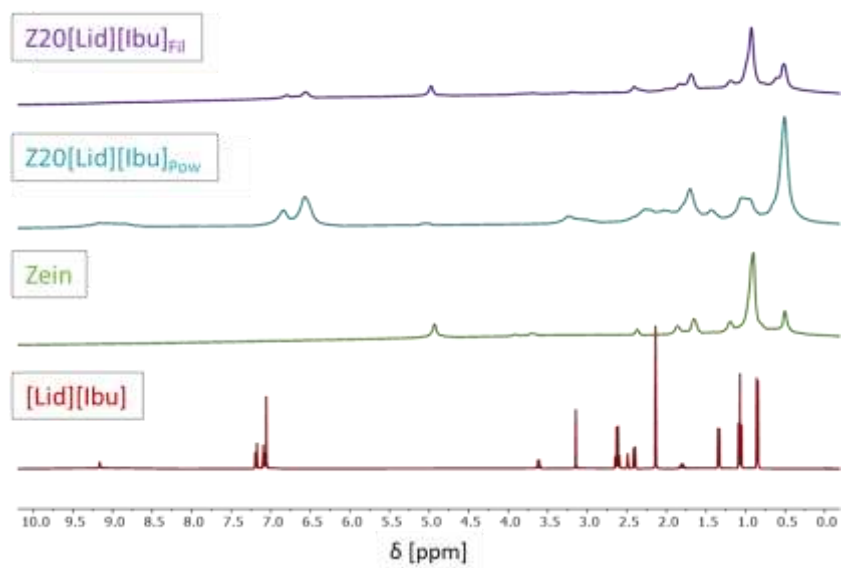


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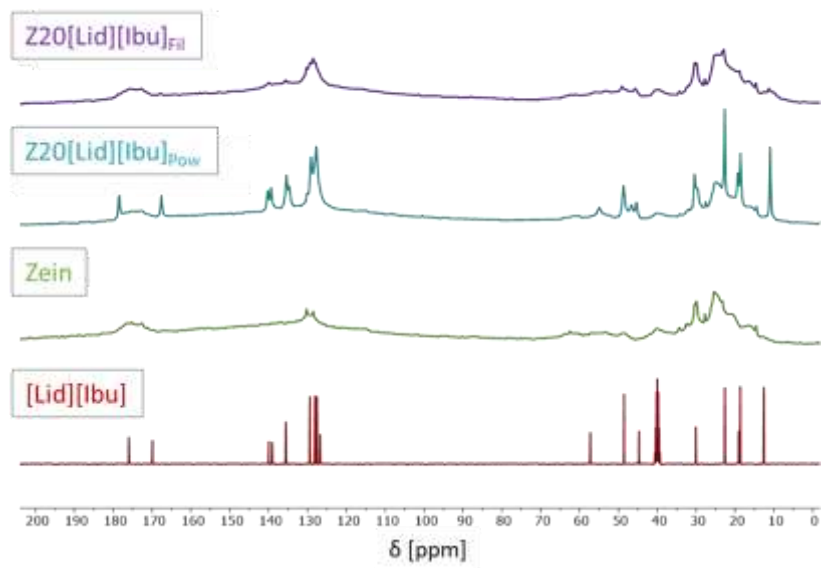
431 **Figure 3.** Chaunier *et al.*

432

a-



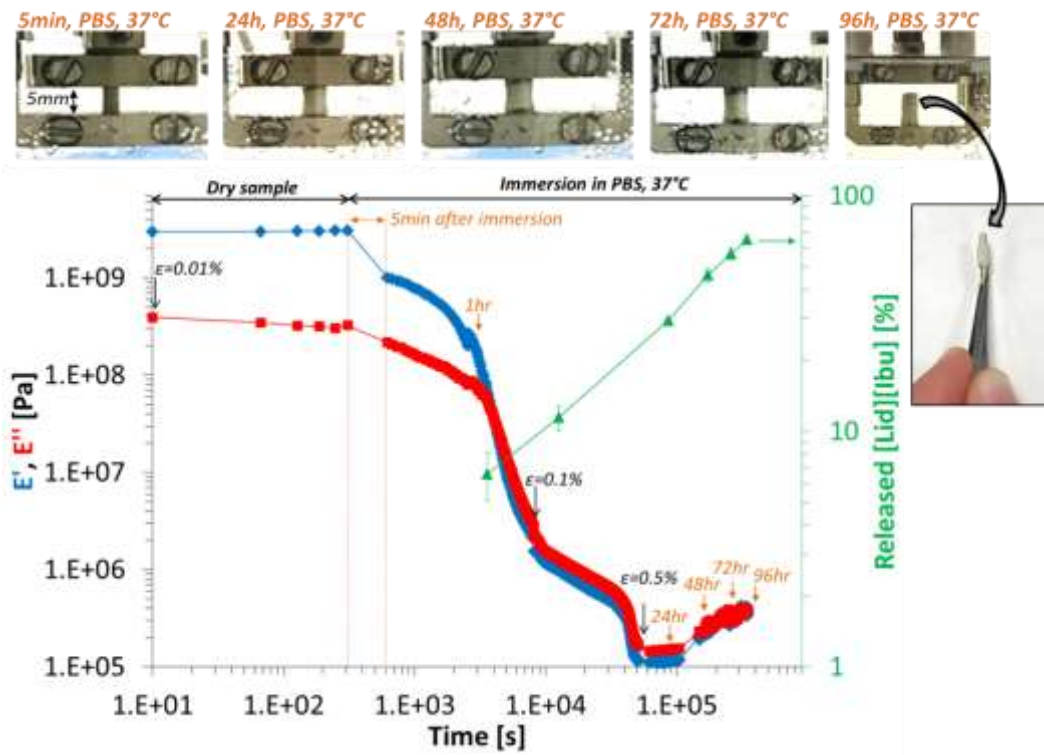
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433

434 **Figure 4.** Chaunier *et al.*

435

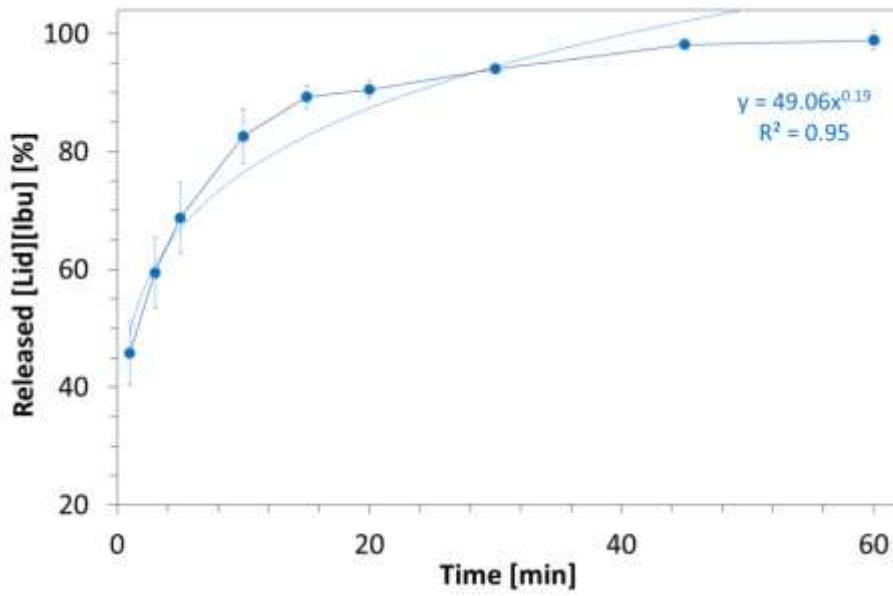


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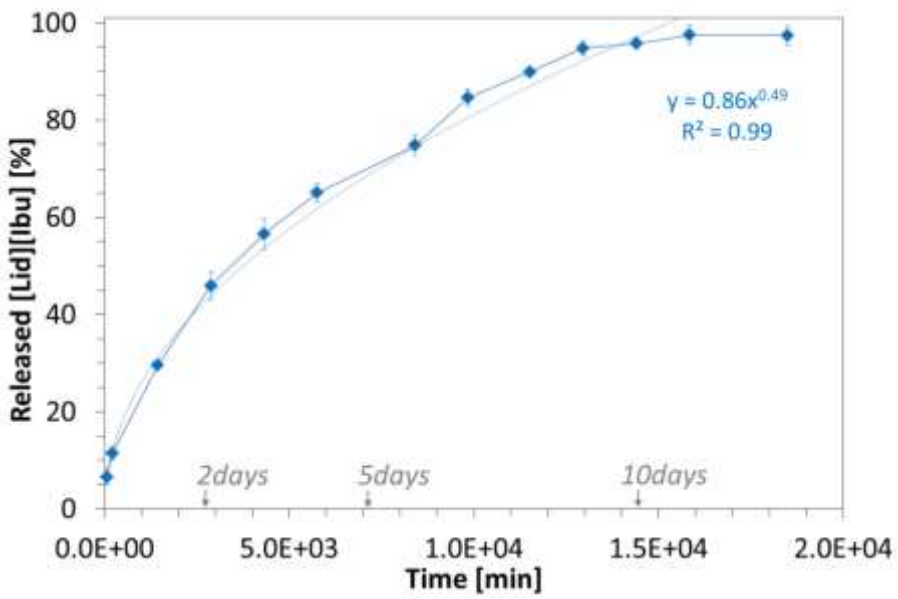
437 **Figure 5.** Chaunier *et al.*

438

a-



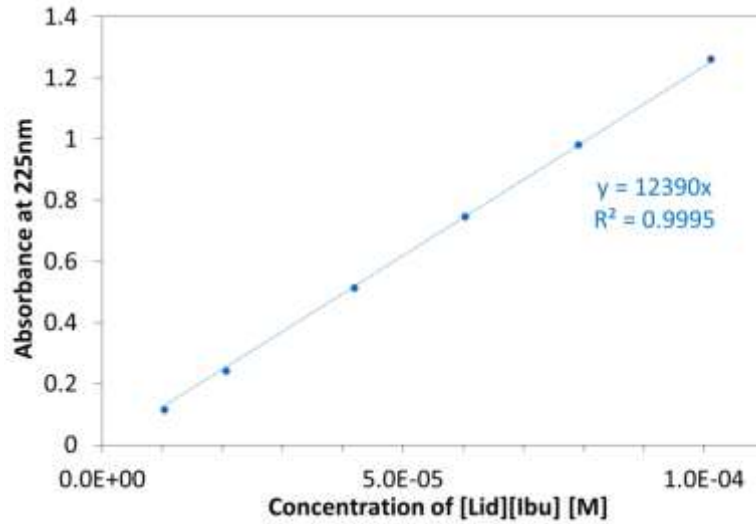
b-



439

440 **Figure 6.** Chaunier *et al.*

441 **Supplementary Data #1 : Evaluation of the released amount of**
 442 **[Lidocainium][Ibuprofenate]**
 443



444 *Figure SD-1. Calibration curve of UV spectroscopy at $\lambda=225\text{nm}$ with PBS solutions of [Lid][Ibu]*

445 The released amount of [Lidocainium][Ibuprofenate] at each dipping time t in 300 mL PBS at
 446 37°C from the powder ($Z20[\text{Lid}][\text{Ibu}]_{\text{Pow}}$), or the extruded sample ($Z20[\text{Lid}][\text{Ibu}]_{\text{Fil}}$), is
 447 calculated as following from aliquot i of 2 mL used for UV analysis:

$$448 \frac{M_t}{M_0} = \left[300 \times \left(\left(\frac{\text{Absorbance}_{\lambda 225\text{nm}i}}{12390} \right) \times M_{[\text{Lid}][\text{Ibu}]} \right) \div M_0 \right] + \int_0^i \left[\left(2 \times \left(\left(\frac{\text{Absorbance}_{\lambda 225\text{nm}}}{12390} \right) \times M_{[\text{Lid}][\text{Ibu}]} \right) \div M_0 \right) \right]$$

449 (Eq. SD-1)

450 with M_t [mg], the amount of [Lid][Ibu] released at instant t ; M_0 , the initial amount of [Lid][Ibu]
 451 [mg]; coefficient 12390 M^{-1} , from the UV calibration curve (Fig. SD-1) and $M_{[\text{Lid}][\text{Ibu}]} = 440.63$
 452 $\text{g}\cdot\text{mol}^{-1}$, the molar mass of [Lid][Ibu].¹²

453 **Supplementary Data #2 : Determination of the specific mechanical energy during the**
454 **extrusion of zein-based filament plasticized by 20w%[Lidocainium][Ibuprofenate] ($\varnothing_{die} =$**
455 **2 mm)**

456

457 The powder mixture, Z20[Lid][Ibu]_{Pow}, is processed with a twin-screw microcompounder
458 (Haake Minilab, Thermo Scientific GmbH ; Karlsruhe, DE) set at a constant screw rotation rate
459 $N = 50$ rpm and 130°C .

460 The average torque is measured during the extrusion of the filament, Z20[Lid][Ibu]_{Fil}, at $T =$
461 0.23 N.m, for a powder mixture feed rate $Q = 1.8$ g.min⁻¹.

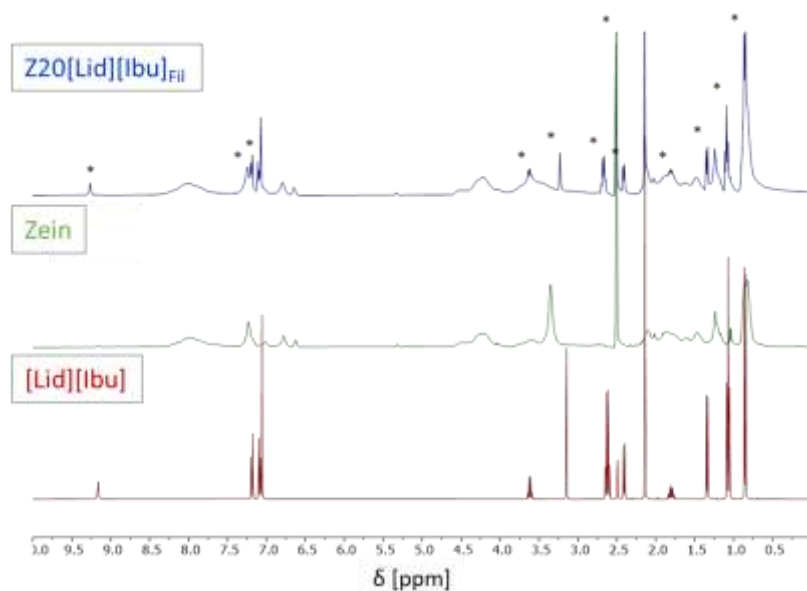
462 The specific mechanical energy, SME [J.g⁻¹], is calculated as following:

463
$$\text{SME} = 2 \cdot \pi \cdot C \cdot N / Q \quad (\text{Eq. SD-2})$$

464 SME is evaluated at about 40 J.g⁻¹.

465 **Supplementary Data #3 : NMR spectra recorded at room temperature in DMSO-d6 of**
466 **extruded filament Z20[Lid][Ibu]_{Fil}, raw zein and pure [Lid][Ibu]**
467

a-



b-

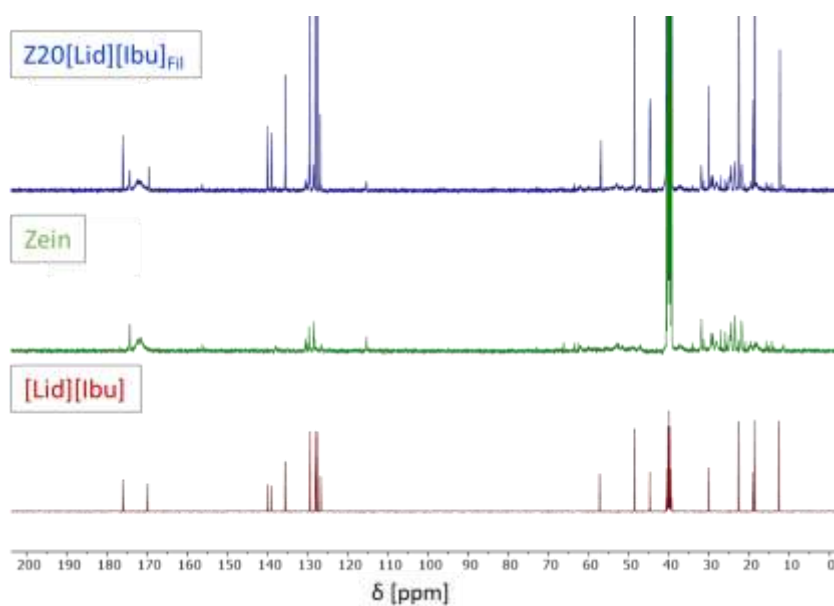
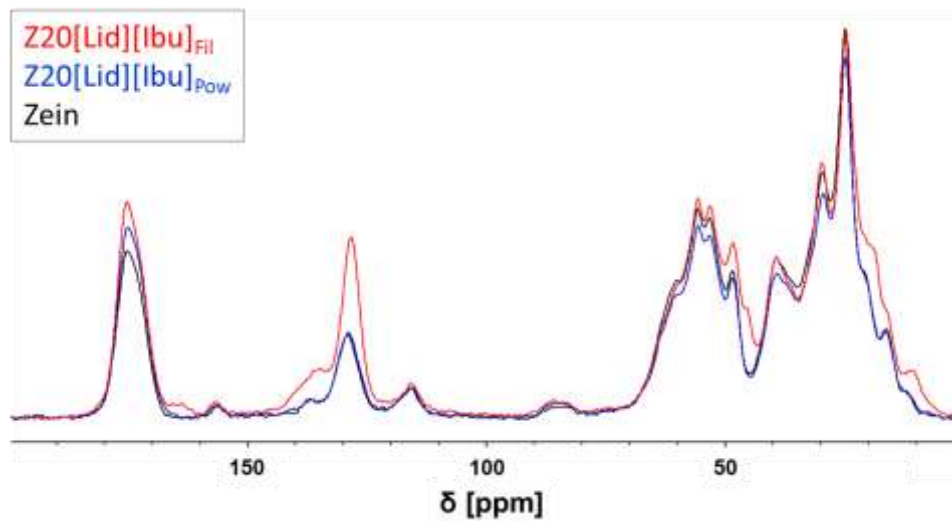


Figure SD-3. Comparison of NMR spectra recorded at room temperature in DMSO-d6 of extruded filament Z20[Lid][Ibu]_{Fil}, raw zein and pure [Lid][Ibu]: ¹H NMR (* corresponds to [Lid][Ibu] signals ; a-) and ¹³C NMR (b-).

468

469 **Supplementary Data #4 : Solid state NMR spectra of extruded filament (Z20[Lid][Ibu]_{Fil}),**
470 **powder blend (Z20[Lid][Ibu]_{Pow}) and raw zein**
471

a-



b-

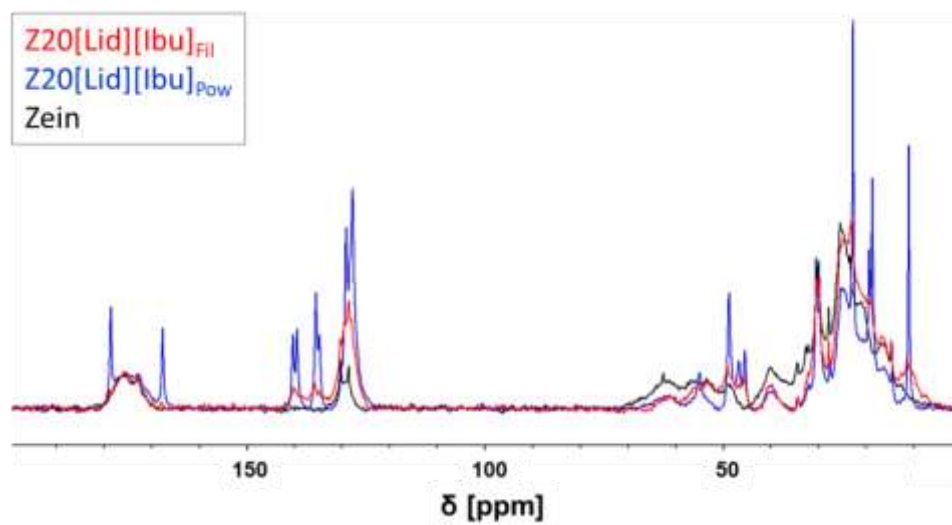


Figure SD-4. Solid state NMR spectra of extruded filament (Z20[Lid][Ibu]_{Fil}), powder blend (Z20[Lid][Ibu]_{Pow}) and raw zein. CP-MAS spectra revealed the rigid part (a-) DP-MAS spectra revealed the mobile part (b-). All spectra areas are standardized compared to the real mass of each sample.

472