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

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Abstract

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

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

1. Introduction

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

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

roles due to its constitutive molecules¹³, with (ii) the cation (Lidocainium) as a local anaesthetic¹⁴ and (iii) the anion (Ibuprofenate) as nonsteroidal anti-inflammatory compound.^{15, 16}

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

In addition, the extrusion of zein with ionic liquids (23% w/w) used as plasticizers was also reported.^{18, 19} However, these works mainly focused on tensile mechanical properties at 25°C of a such amphiphilic matrix.²⁰ The use of a commercial imidazolium ionic liquid (1-butyl-3-methyl imidazolium chloride: [BMIM][Cl]) leads to plasticized zein with rubber like behaviour (Elastic modulus < 10 MPa and Elongation at break > 400%).^{18, 19} Concurrently, plasticization with a synthesized cholinium acetate ionic liquid leads to more rigid and brittle behaviour (Elastic modulus > 180 MPa and Elongation at break < 10%).¹⁹

In the present work, we describe the extrusion of zein plasticized by 20w% [Lidocainium][Ibuprofenate] ([Lid][Ibu]), as an alternative process to conventional galenics, such as powder compression or soluble capsules gelation, for obtaining drug delivery systems. The objective is to take advantage of expected plasticizing effect of the pharmaceutically active ionic liquid to hot melt process zein by extrusion, in order to obtain calibrated parts containing a high degree of ingredients mixing.

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

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

2. Experimental section

2.1. Raw materials

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

2.2. Powder blend, extrusion and storage of the extrudates

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

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

2.3. Characterizations

2.3.1. Thermogravimetric Analysis (TGA)

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

2.3.2. *Dynamic Mechanical Thermal Analysis (DMTA)*

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

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

2.3.3. *Differential scanning calorimetry (DSC)*

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

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

2.3.4. Wide Angle X-ray Scattering (WAXS)

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

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

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

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

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

2.3.6. Liquid state NMR

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

2.3.7. In vitro release

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

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

3. Results and discussion

3.1. Thermal stability

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

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

3.2. Filaments processing and thermomechanical properties

The extrusion is carried out at 130°C with the microcompounder to obtain filaments, Z20[Lid][Ibu]_{fil}, as straight cylinders ($\varnothing_{\text{filament}} \approx 2\text{mm}$), with an average specific mechanical energy (SME) measured at about 40 J.g⁻¹ during processing (please see the Supplementary Data #2 section). The filaments appear as stable monoliths after extrusion, without phase separation. They are rigid at ambient conditions, after storage at stable relative humidity of 59 % during one week, with a storage modulus E' measured by DMTA at about 3 GPa at 20°C (Fig.2-a). They present a main mechanical relaxation which onset, T_{α_onset}, is found at about 55°C. Comparatively, the previously reported plasticization of zein by a [BMIM][Cl] commercial ionic liquid had shown much lower values of E' at 20°C (≈ 0.2 GPa) due to a mechanical relaxation starting at lower temperature (T_{α_onset} ≈ -10°C).¹⁸ Despite the glass transition temperature T_g was not measured in this earlier work, this suggests that [BMIM][Cl] should be a more efficient glass transition temperature depressor than [Lid][Ibu]. For this later point, the glass transition results in a drop of the heat flow measured by DSC from 10 to 70°C (Fig.2-b). In this broad range, the midpoint glass transition temperature is estimated at 53°C. This glass temperature of the blend is in between those of the pristine two components : Pure [Lid][Ibu] shows a glass transition at -30°C, while the one of the raw zein is found at 77°C (Fig.2-b). This suggests that their blend is miscible. The application of the Fox law supports this assumption²¹ :

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

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

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

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

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

3.3 Structural characterization

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

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

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

3.4. Ionic liquid mobility

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

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

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

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

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

3.5. Mechanical properties and release abilities in simulated physiological conditions

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

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

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

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

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

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

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

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

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

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 and $a \cdot \alpha_n$ the zeros of this function.

The diffusion coefficient is computed at $D = 2.9 \cdot 10^{-13} \text{ m}^2 \cdot \text{s}^{-1}$, with $M_t/M_0 = 0.57$, after 72h immersion of filaments in PBS at 37°C. This value is less important than a hot melt processed

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

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

4. Conclusion

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

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Figure captions

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

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

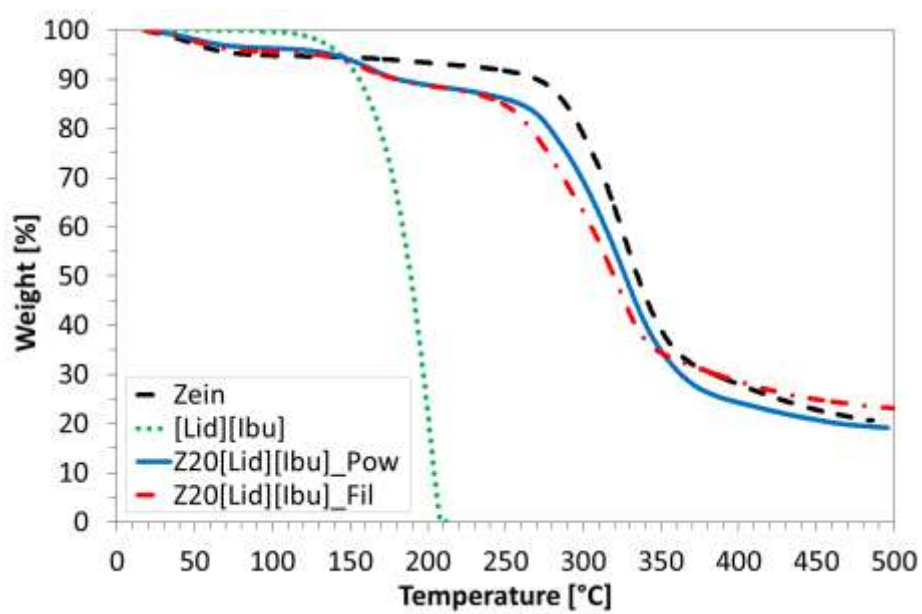
Figure 3. WAXS diffractograms obtained on the raw zein, the powder blend Z20[Lid][Ibu]_{Pow} and after extrusion Z20[Lid][Ibu]_{Fil}.

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

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

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

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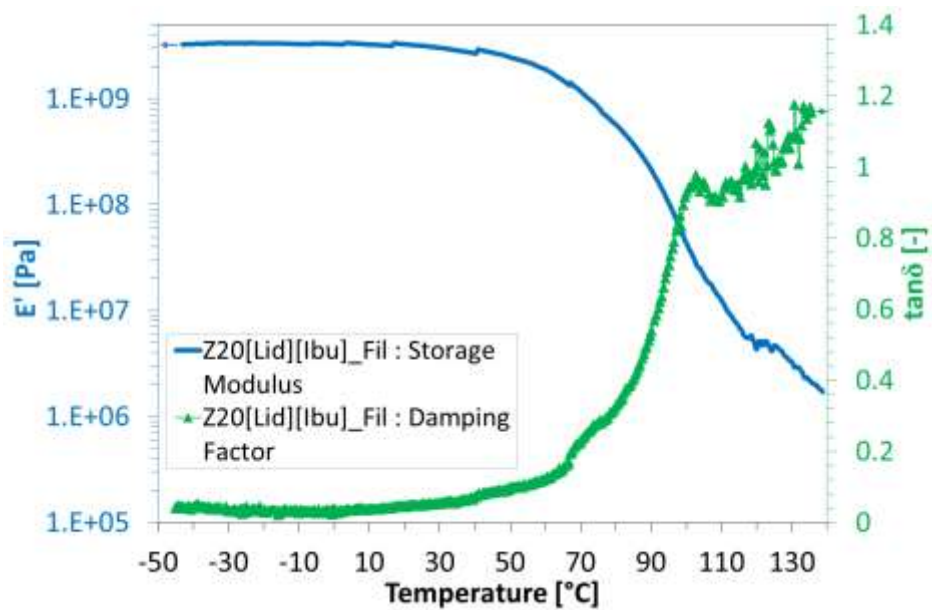


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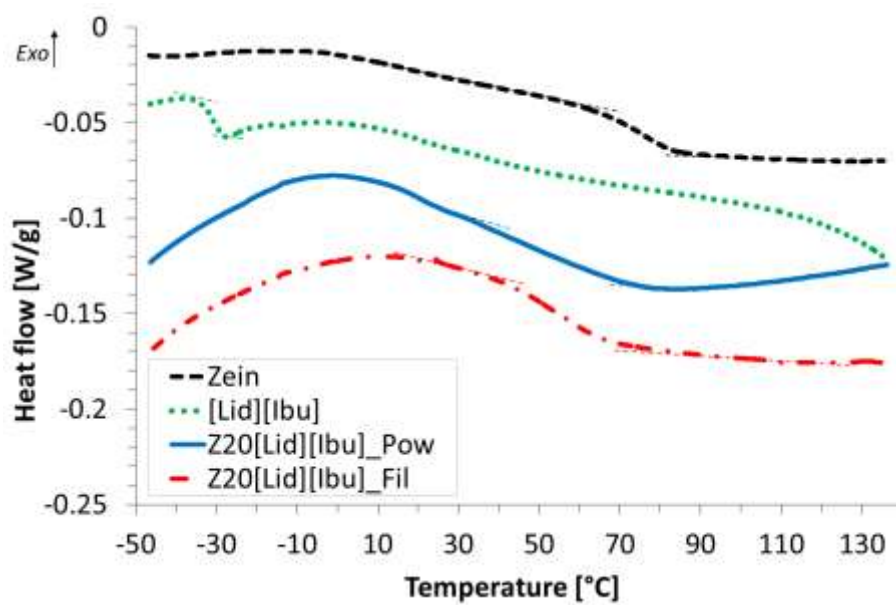
425 **Figure 1.** Chaunier *et al.*

426

a-



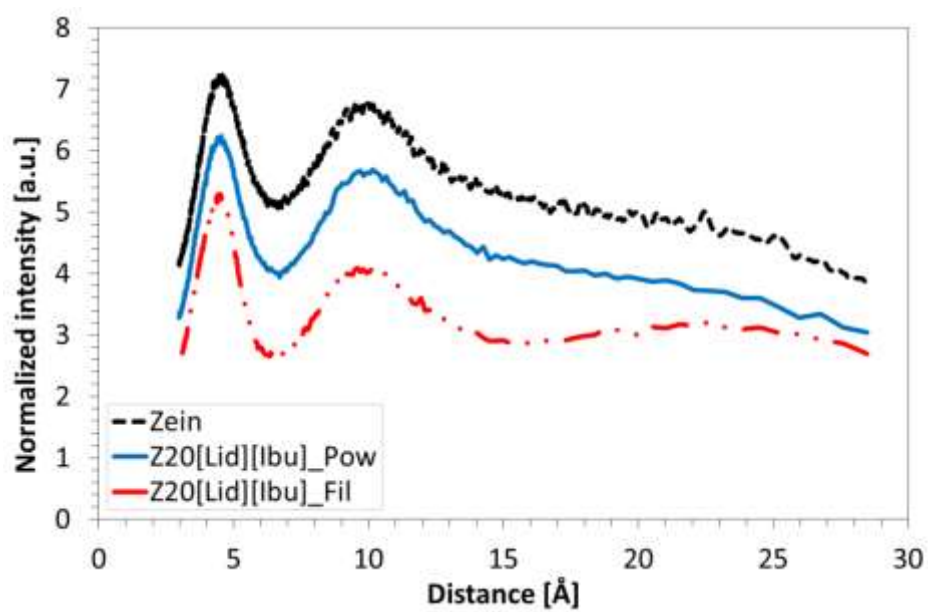
b-



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

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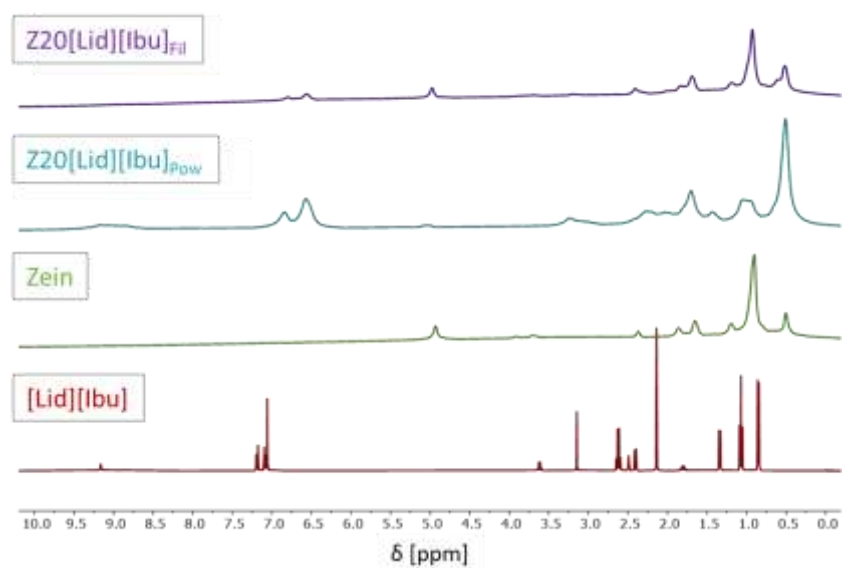


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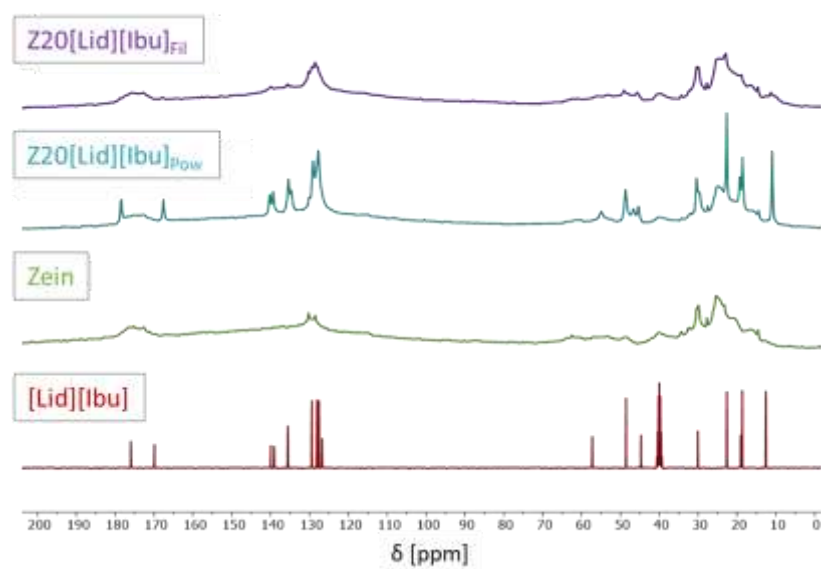
431 **Figure 3.** Chaunier *et al.*

432

a-



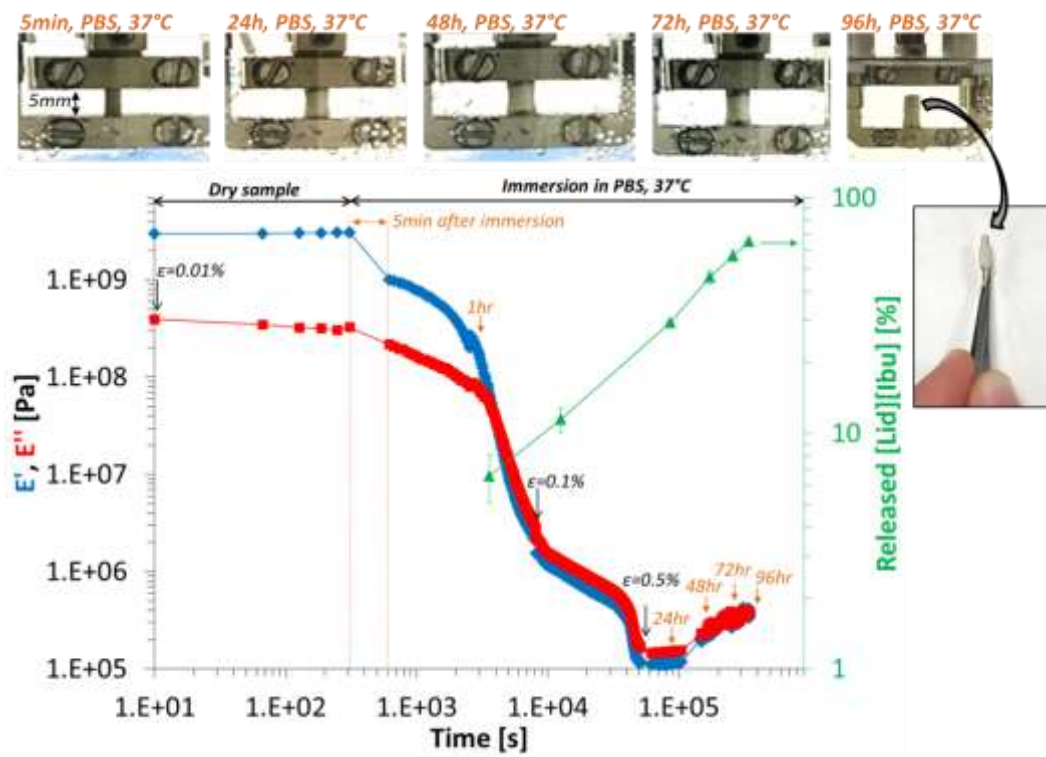
b-



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

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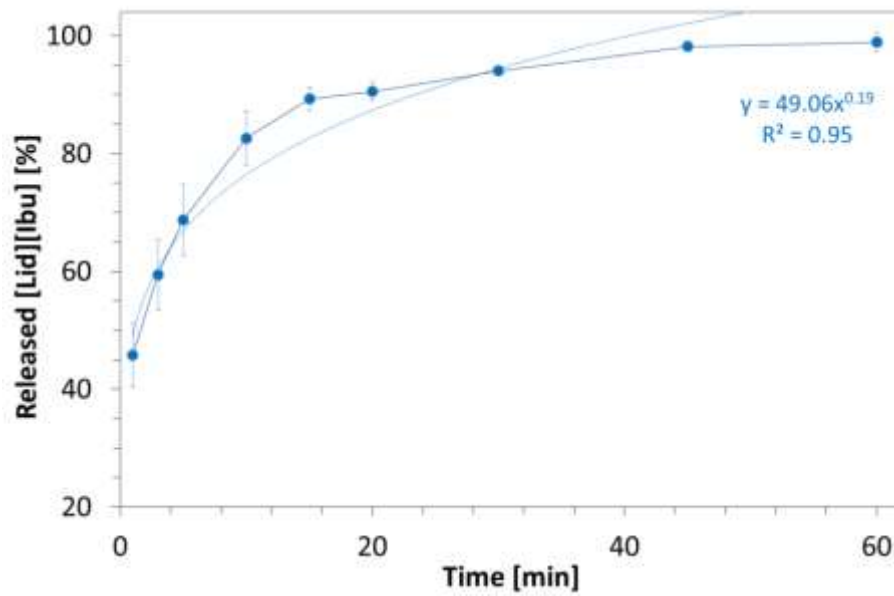


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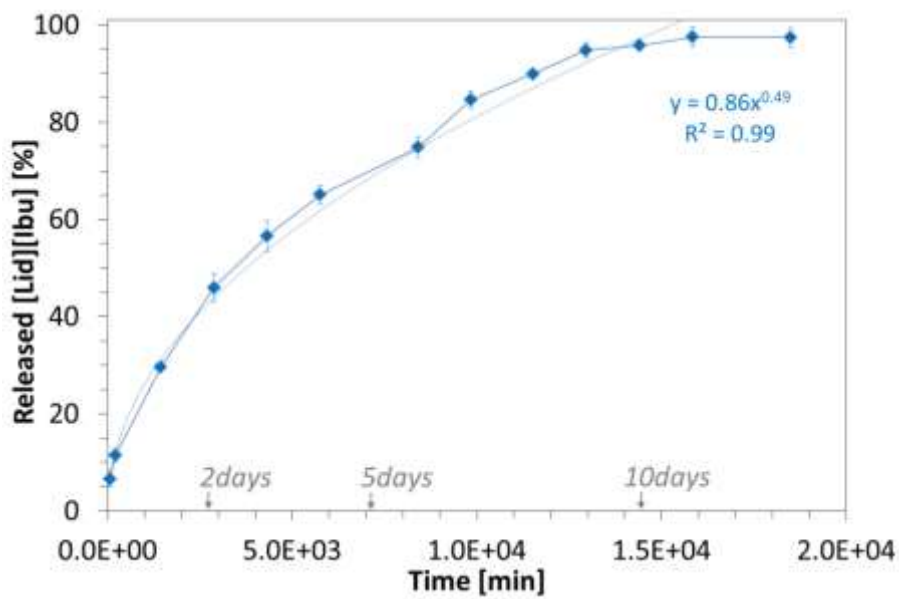
437 **Figure 5.** Chaunier *et al.*

438

a-



b-



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

Supplementary Data #1 : Evaluation of the released amount of [Lidocainium][Ibuprofenate]

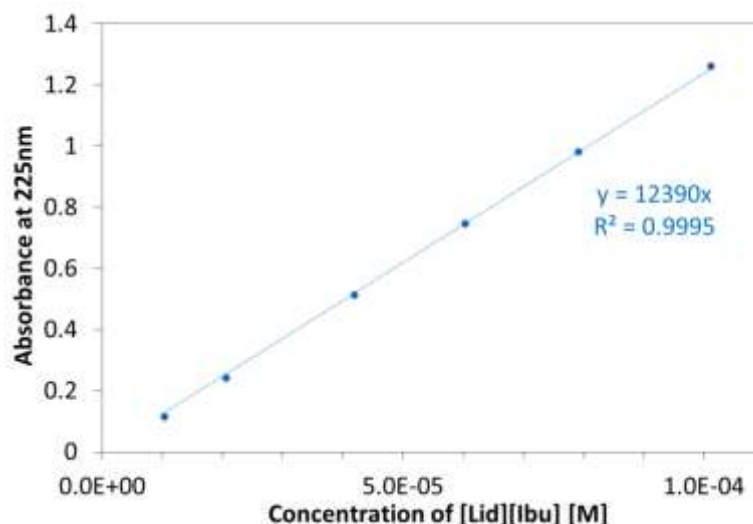


Figure SD-1. Calibration curve of UV spectroscopy at $\lambda=225\text{nm}$ with PBS solutions of [Lid][Ibu]

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

$$\frac{M_t}{M_0} = \left[300 \times \left(\left(\frac{\text{Absorbance}_{\lambda 225\text{nm}i}}{12390} \right) \times M_{[\text{Lid}][\text{Ibu}]} \right) \div M_0 \right] + \int_0^i \left[\left(2 \times \left(\left(\frac{\text{Absorbance}_{\lambda 225\text{nm}}}{12390} \right) \times M_{[\text{Lid}][\text{Ibu}]} \right) \div M_0 \right) \right] \quad (\text{Eq. SD-1})$$

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

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

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

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

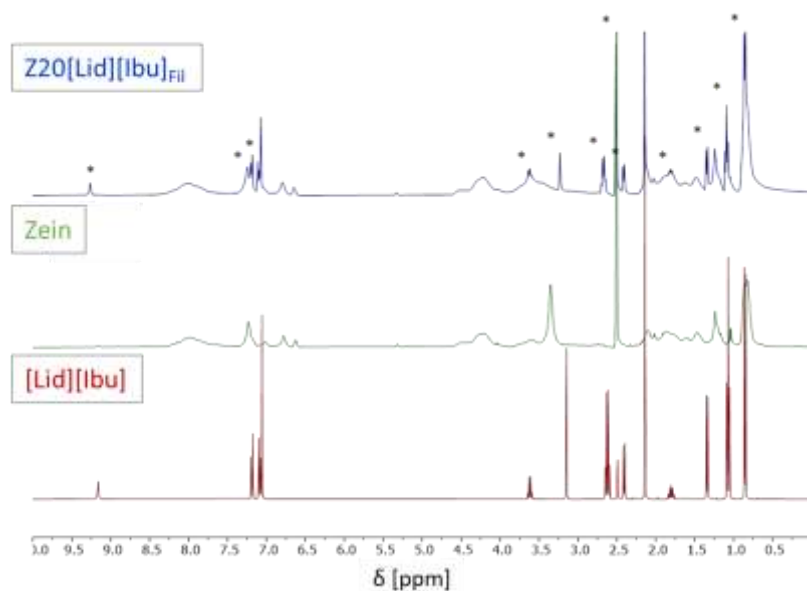
The specific mechanical energy, SME [J.g^{-1}], is calculated as following:

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

SME is evaluated at about 40 J.g^{-1} .

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

a-



b-

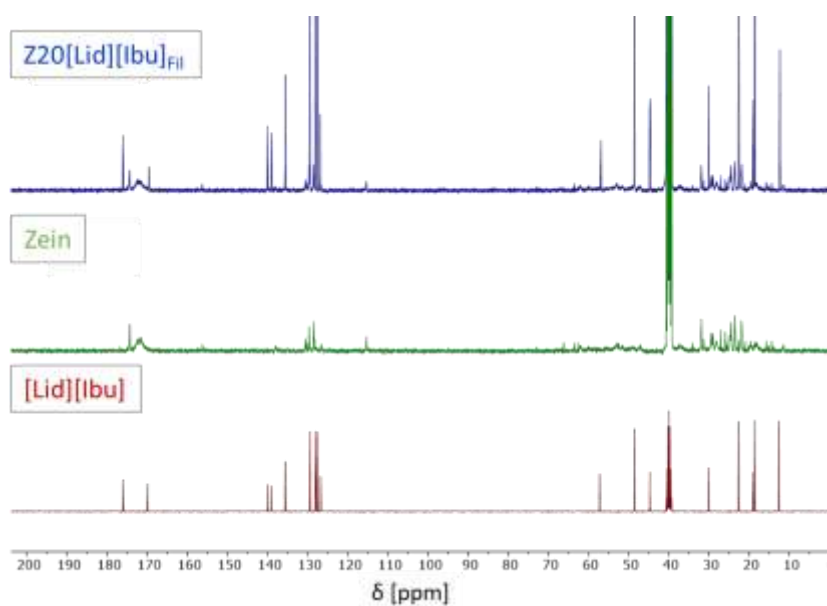
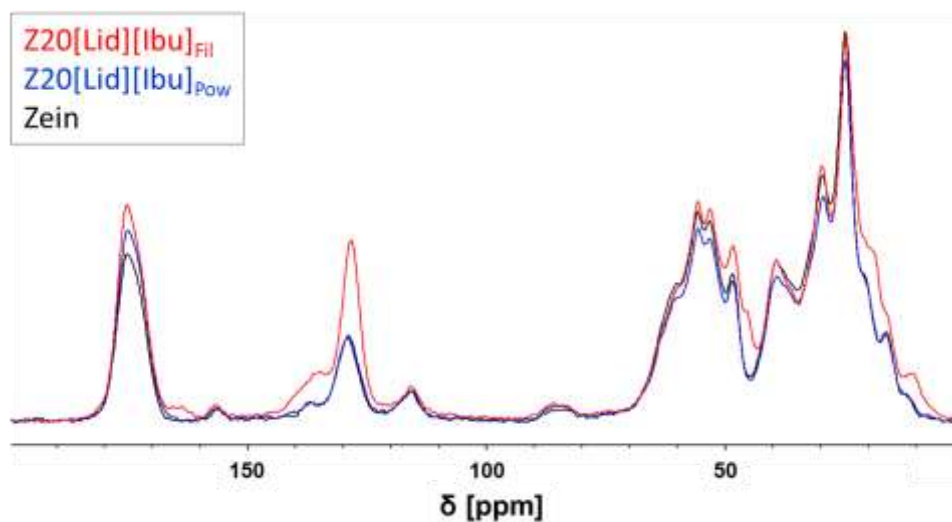


Figure SD-3. Comparison of NMR spectra recorded at room temperature in DMSO-d₆ of extruded filament Z20[Lid][Ibu]_{Fil}, raw zein and pure [Lid][Ibu]: ¹H NMR (* corresponds to [Lid][Ibu] signals ; a-) and ¹³C NMR (b-).

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

a-



b-

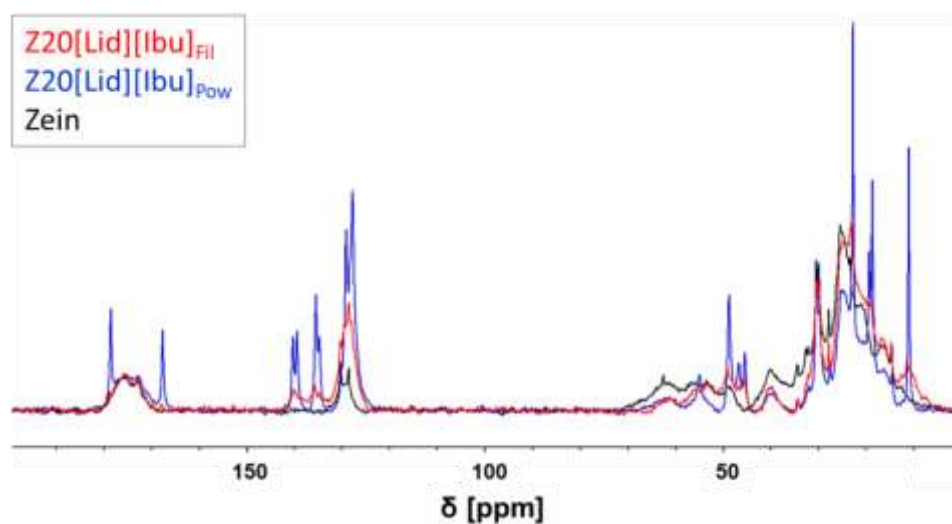


Figure SD-4. Solid state NMR spectra of extruded filament (Z20[Lid][Ibu]_{Fil}), powder blend (Z20[Lid][Ibu]_{Pow}) and raw zein. CP-MAS spectra revealed the rigid part (a-) DP-MAS spectra revealed the mobile part (b-). All spectra areas are standardized compared to the real mass of each sample.