



HAL
open science

Cost-efficient polyurea carrier for precise control of an anti-inflammatory drug loading and release

Gabriele A. Pedroza, Lucia H. G. M. C. Macedo, Ricardo de Oliveira Bordonal, Natalia N. Silveira, Renato P. Orenha, Renato L. T. Parreira, Raquel A. dos Santos, Yann Molard, Maria Amela-Cortes, Eduardo F. Molina

► To cite this version:

Gabriele A. Pedroza, Lucia H. G. M. C. Macedo, Ricardo de Oliveira Bordonal, Natalia N. Silveira, Renato P. Orenha, et al.. Cost-efficient polyurea carrier for precise control of an anti-inflammatory drug loading and release. *Journal of Drug Delivery Science and Technology*, 2022, 76, pp.103744. 10.1016/j.jddst.2022.103744 . hal-03798136

HAL Id: hal-03798136

<https://hal.science/hal-03798136v1>

Submitted on 16 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Journal Pre-proof

Cost-efficient polyurea carrier for precise control of an anti-inflammatory drug loading and release

Gabriele A. Pedroza, Lucia H.G.M.C. Macedo, Ricardo de Oliveira, Natália S. Nascimento, Renato P. Orenha, Renato L.T. Parreira, Raquel Santos, Yann Molard, Maria Amela-Cortes, Eduardo F. Molina

PII: S1773-2247(22)00655-4

DOI: <https://doi.org/10.1016/j.jddst.2022.103744>

Reference: JDDST 103744

To appear in: *Journal of Drug Delivery Science and Technology*

Received Date: 2 May 2022

Revised Date: 17 August 2022

Accepted Date: 22 August 2022

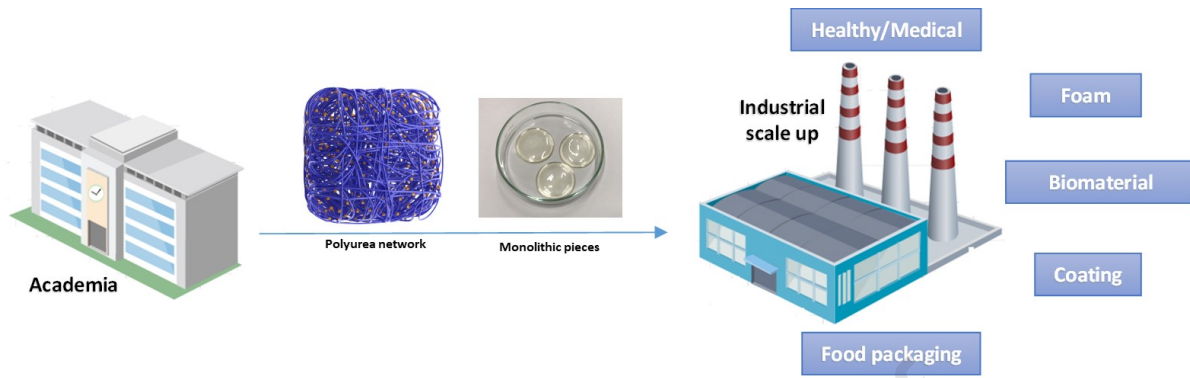
Please cite this article as: G.A. Pedroza, L.H.G.M.C. Macedo, R. de Oliveira, Natá.S. Nascimento, R.P. Orenha, R.L.T. Parreira, R. Santos, Y. Molard, M. Amela-Cortes, E.F. Molina, Cost-efficient polyurea carrier for precise control of an anti-inflammatory drug loading and release, *Journal of Drug Delivery Science and Technology* (2022), doi: <https://doi.org/10.1016/j.jddst.2022.103744>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier B.V.



Graphical abstract



Journal Pre-proof

1 **Cost-efficient Polyurea Carrier for Precise Control of an anti-inflammatory**

2 **Drug Loading and Release**

3 *Gabriele A. Pedroza,¹ Lucia H. G. M. C. Macedo,¹ Ricardo de Oliveira,¹ Natália S. Nascimento,¹*

4 *Renato P. Orenha,¹ Renato L. T. Parreira,¹ Raquel Santos,¹ Yann Molard,² Maria Amela-Cortes,²*

5 *Eduardo F. Molina*¹*

6
7 ¹*Universidade de Franca, Av. Dr. Armando Salles Oliveira 201, 14404-600 Franca, SP, Brazil*

8 ²*Université Rennes, CNRS, ISCR - UMR 6226, ScanMAT – UMS 2001, F-35000 Rennes, France*

10
11 Corresponding author: Eduardo F. Molina

12 *email: eduardo.molina@unifran.edu.br

13 ORCID : 0000-0002-3574-2923

14

15

16

17

18

19

20

21

22

Abstract

23 In this paper, we present a cost-efficient and reliable route to produce polyurea xerogel (PolyU) as a
24 versatile carrier that provides a high drug loading and offers a tuning over diclofenac (DCF) release
25 profile. A simple one-pot reaction of an amino-terminated-polyether-PEO and a crosslinker,
26 hexamethylene diisocyanate trimer-HDI, allow us to obtain the polymeric networks. The gelation
27 time during the sol-gel reactions (hydrolysis and condensation) can be modulated from minutes to
28 hours by using acetone as solvent to achieve a decrease of reactivity between amine groups from
29 PEO with isocyanate from HDI crosslinker. The interactions of PolyU networks and DCF drug was
30 in depth evaluated by Fourier Transform Infrared Spectroscopy (FTIR), small angle X-ray
31 scattering (SAXS) and computational studies. Analysis performed by differential scanning
32 calorimetry (DSC) have confirmed the inhibition of crystalline moieties of PEO by drug interactions
33 with the PEO chains. PolyU was investigated in cell toxicity studies, showing no significant
34 cytotoxicity against the CHO-K1 cell line. Considering the abundance of raw materials and cost-
35 efficient for polyurea preparation, this work clearly opens up high prospects and provides a solution
36 for scaling up the fabrication of new functional devices (contact lenses, patches, thin films, etc)
37 with broad applications in the medical/health fields.

38 *Keywords: sol-gel, polyetheramine, isocyanate crosslink, microphases, small angle X-ray*
39 *scattering.*

40

41

42

43 1. Introduction

44 Polymer derivated materials are usually applied as carrier for delivery and control release of
45 drugs [1], proteins [2], therapeutic compounds [3], inorganic particles [4] showing advanced
46 functions such as imaging agents for analytics and diagnostics [5], targeted delivery [6], controlled
47 encapsulation [7], and more. However, the methodology used to produce these materials are often
48 not economically viable and do not meet the requirements for production on an industrial scale.
49 Therefore, many efforts have been made aiming to develop such carrier technologies by using, for
50 example, electrospinning [8] or microfluidic [9] methods that allow a fine control over their
51 monodispersity, structures, and compositions.

52 Polyurea is an elastomer polymer obtained from the reaction of polyamines and
53 polyisocyanates resulting in the formation of urea linkages (-NH-CO-NH-) [10]. This class of
54 polymer receives continuous attention from the scientific community, in particular, due to i) the
55 absence of a catalyst during the reactions [11], ii) its high thermal/chemical stability [12,13], ii) its
56 facile processability and iv) its resistance to UV radiation [14]. Polyurea elastic network shows
57 microphase separation of two immiscible, covalently connected components, known as “hard” and
58 “soft” domains. The “hard” domains act as physical cross-linker to reinforce the elastomer, while
59 the “soft” domains form the continuous phase provide elasticity [15]. Furthermore, polyurea
60 networks exploiting the hydrogen-bonding directionality (i.e. well-defined secondary structures) are
61 of particular interest as supramolecular polymers [16-18].

62 Zhang et. al [12] produced new polyurea thin-film membranes for extreme pH
63 nanofiltration. The fabricated membranes, based on branched polyethyleneimine, piperazine, and
64 multi-isocyanate monomers, showed excellent acid/alkali resistance after exposure to HCl, H₂SO₄
65 and NaOH solutions (20 wt/v%) and are suitable for the treatment of industrial wastewater. By
66 using commercially available reagents, Paraskevopoulou et al. [19] obtained polyurea-crosslinked
67 calcium alginate beads (X-Ca-alg). The authors reported that X-Ca-alg biopolymers are robust
68 materials compared to conventional Ca-alginate aerogels that are mechanically weak, and have

69 practical applications including environmental remediation. In another work, polyurea was used as
70 microcapsule to incorporate phexim pesticide for agriculture purposes. The phoxim-loaded polyurea
71 showed high UV-resistance ability and can prolonge the effective duration of pesticide. It may be
72 also applied as microcapsule for others pesticides [14].

73 Reports of polyurea as carrier for drug delivery systems are scarce [20-23]. In this work, we
74 present a facile preparation of a polyurea xerogel with capacity to incorporatate high amounts (up to
75 30 wt%) of an anti-inflammatory drug. Diclofenac sodium (DCF) was chosen for this study. It has
76 both analgesic and antipyretic properties and is classically used for the treatment of degenerative
77 joint diseases such as rheumatoid arthritis, osteoarthritis. Administrated by ocular route, it is used in
78 the management of ocular pathologies treated by surgery. Its low biological half-life (1 or 2 hours)
79 implies multiple dosing to keep its therapeutic blood level, which often leads to adverse side effects
80 in a long-term administration such as gastrointestinal bleeding, disturbances or peptic ulceration.
81 Therefore, its controled release should provide extended therapeutic benefits with minimal local
82 irritation.

83 The polyurea obtained in this work is a low-cost material that contains flexible
84 polyetheramine blocks connected to an isocyanate trimer to form urea linkages. It is produced by a
85 facile one-pot sol-gel reaction, which is a scalable, powerful and economically viable method,
86 offering fine control over structure and loaded amount of drugs. The objectives of this work are to
87 investigate in depth the i) visual polyurea gelation time as a function of monomers contact time with
88 a solvent, ii) the biocompatibility of the matrix through citotoxicity studies, iii) the influence of the
89 drug content on the structure of polyurea, iv) the release profile and kinetic mechanisms as a
90 function of drug load. In particular, we show that the diclofenac drug release profile can be
91 modulated by the interactions between DFC drug and the polyurea matrix as well as by the loaded
92 drug amount.

93

94

95

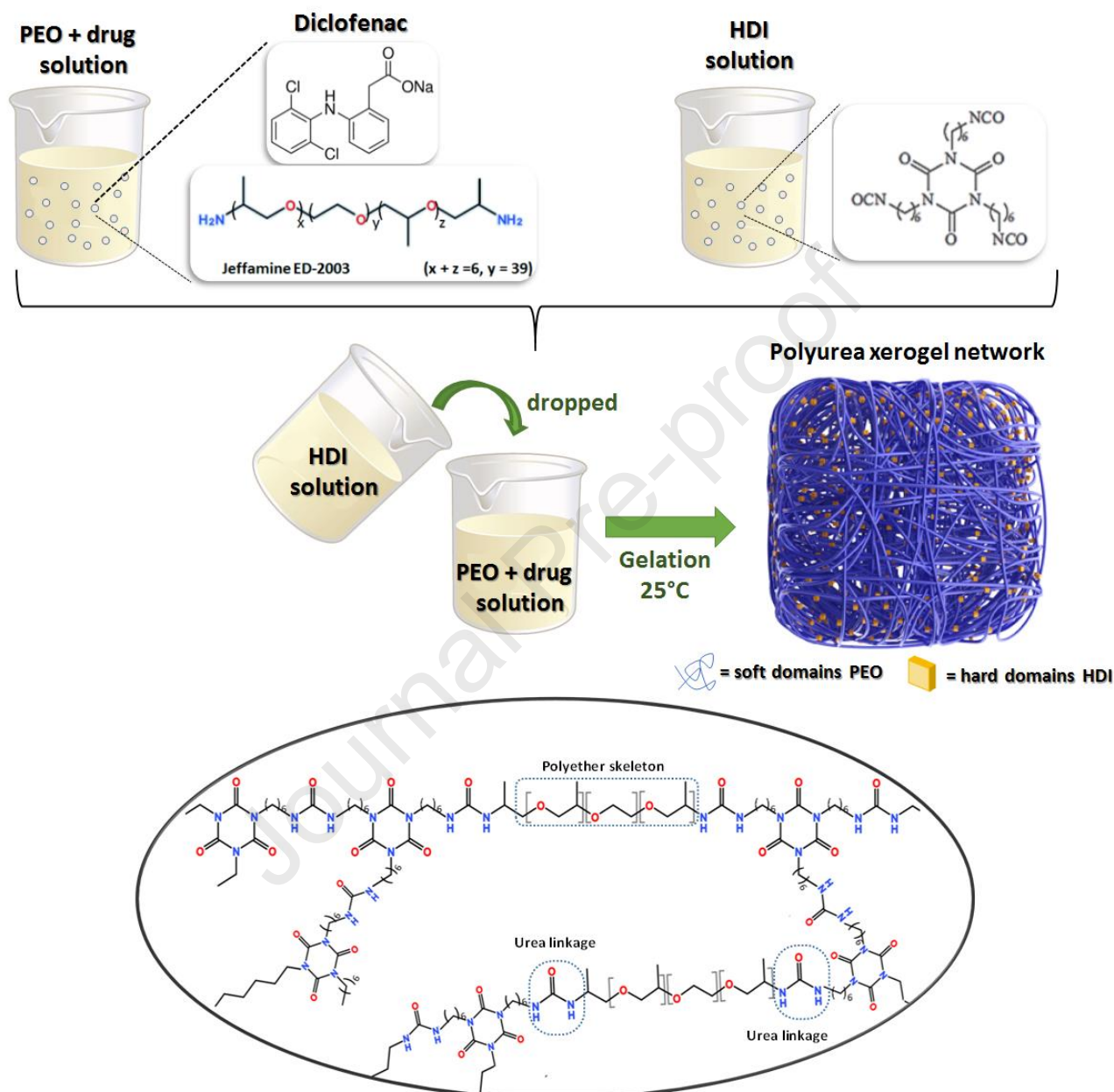
96 2. Experimental and characterizations

97 *2.1 Materials:* Diclofenac sodium salt DCF ($C_{14}H_{10}Cl_2NNaO_2$) and acetone (ACS reagent, $\geq 99.5\%$)
98 were purchased from Sigma-Aldrich. O,O'-bis-(2-aminopropyl)polypropylene glycol-block-
99 polyethylene glycol-block-polypropylene (Jeffamine ED2003 - PEO block with a molecular weight
100 of 1900 g mol^{-1}) and the hexamethylene diisocyanate trimer-HDI (Desmodur N3300 with a
101 molecular weight of $\sim 504\text{ g mol}^{-1}$) were donated by Huntsman Performance Products (Brazil) and
102 Bayer Corporation, respectively. The Jeffamine ED2003 and Desmodur N3300 are reagents
103 commercially available from Huntsman and Bayer. All reagents were used without further
104 purification.

105 *2.2 Synthesis of polyurea gels:* The polyurea xerogel was obtained by organic polycondensation
106 reaction (sol-gel process) as reported in literature [24-26]. In brief, tridentate ligand HDI was
107 covalently bonded to the PEO (Jeffamine ED-2003) by reaction of the isocyanate groups of HDI
108 and the primary amino groups attached to the end of the polyether backbone of PEO (**Scheme 1**). In
109 brief, 4 g of PEO macromer ($2.10 \times 10^{-3}\text{ mol}$) and 1 g of HDI cross-linker ($1.98 \times 10^{-3}\text{ mol}$) were
110 completely dissolved using acetone in two separated beakers. These were sealed and stirred for 2h,
111 at room temperature ($\sim 25^\circ\text{C}$), to form a homogenous solutions. The HDI solution was added
112 dropwise to the PEO solution, while stirring at room temperature, until complete dissolution. The
113 resulting solution was poured into Teflon[®] mold and kept at 25°C for 24 h for gelation.

114 *2.3 Synthesis of polyurea gels containing diclofenac drug:* Polyurea samples containing DCF were
115 prepared *via* one-step sol-gel process. The desired drug amount (from 1 to 30 wt% with respect to
116 the mass of PEO) was dissolved in acetone and then mixed with PEO to obtain a homogeneous
117 solution. The HDI solution was dissolved in a separated beaker and added as cited above to form
118 DCF-loaded polyurea samples. The resulting mixture was poured into Teflon[®] mold and gelled
119 using the same conditions (temperature and time) than for the pure polyurea. The final materials
120 were named PolyU (polyurea xerogel), PolyU-DCF_x (loaded polyurea containing diclofenac DCF

121 and x for the wt% of drug loaded). Regardless of the polyurea sample (loaded and unloaded) the
 122 obtained membranes were transparent and flexible. Formulations of the polyurea samples without
 123 and containing diclofenac drug percentage from 1 to 30 wt% are presented in **Table S1**.



124

125

126

127 2.4 Characterization:

128

Fourier Transform Infrared Spectroscopy FTIR spectra was recorded at 3100-700 cm^{-1}

SCHEME 1

129 by ATR mode using a Perkin Elmer Frontier spectrometer, with a resolution of 4 cm^{-1} and average
130 of 12 scans.

131 **Small angle X-ray scattering SAXS** experiments were conducted using a Nano-InXider
132 (Xenocs). X-rays of wavelength $\lambda = 1.54\text{ \AA}$ was used, and the measurements was performed at
133 sample-to-detector distance of 938 mm to cover a q -range of $0.009 < q < 0.45\text{ \AA}^{-1}$, where $q = (4$
134 $\pi/\lambda) \sin(\theta/2)$ corresponding to the magnitude of the scattering vector, and θ is the scattering angle.
135 Beam size on sample: $400\text{ }\mu\text{m}$ (0.4 mm), typical flux: 60 Mph/s , and $Q_{\text{min}}: 0.0044\text{ \AA}^{-1}$. All the
136 measurements were recorded at room temperature ($\sim 25\text{ }^\circ\text{C}$) using a cell window under vacuum. To
137 collect the SAXS pattern, samples with $1.8\text{ mm} \pm 0.10$ (thickness) and 20 mm^2 (area) were used.

138 **Visual determination of gel time:** In order to evaluate the reactivity (gelation time) of the
139 polyetheramine-PEO and isocyanate HDI, acetone was used as solvent for capping the amines of
140 the polymer chains. In this sense, after the total solubilization of PEO and HDI (separately) the
141 influence of polymer/isocyanate solution contact time with acetone before condensation reaction
142 was studied. The volume of acetone to solubilize PEO and HDI was 7 and 5 mL, respectively.
143 Gelation was considered when the particles present in the initial sol rigidifies the whole wet sol
144 medium. Specifically, condensation reaction was induced by HDI solution added dropwise to the
145 PEO solution. Shortly thereafter, the mixed PEO-HDI solution was spread in an acrylic plate
146 covered by Teflon® using a film extensor. A glass slide was placed on the film without pressure.
147 The gel time was considered when the sol sharply decreased its viscosity converting a viscous
148 liquid state to a gel. The visual experiments were performed on two independent samples, and the
149 results are presented as the data average.

150 **Differential scanning calorimetry DSC** was used to evaluate the influence of drug
151 content on the glass transition temperature and fusion temperature of crystalline PEO domains. DSC
152 measurements were made using a TA25 DSC. Disk shape of approximately 10 mg were cut off
153 from the polyurea membranes and placed in $40\text{-}\mu\text{L}$ aluminium containers. Each sample was heated
154 from -80 to $250\text{ }^\circ\text{C}$ at rate of $10\text{ }^\circ\text{C min}^{-1}$ using argon as the purge gas.

156 **Computational methods:** the geometry optimization of all compounds was performed
157 without constraints and the vibrational frequencies were calculated using the B97D3, [27,28]
158 functional and the 6-31+G(2d,p) basis set (**Table S2**) [29-31]. The 6-31+G(2d,p) basis set
159 provides a good accuracy/efficiency relationship for organic complex systems [32]. Vibrational
160 analyses for all optimized geometries confirm that they are all energy minima at the computational
161 model applied here. Importantly, the molecular electrostatic potential (MEP) [33] surfaces of the: i)
162 isolated drug (diclofenac); and ii) structures derived from polymer polyurea (I-III), were calculated
163 for aid in the choice of the conformations of the complexes investigated (**Figure S1**). These
164 calculations were made using the Gaussian 16 (Revision A.03) software [34]. The bonding
165 mechanism was elucidated through the energy decomposition analysis (EDA) [35] using the BLYP
166 [36,37] functional and Grimmes D3 dispersion correction with Becke-Johnson damping function
167 (D3(BJ)) [38] combined with the TZ2P [39] basis set. These calculations were realized with the
168 ADF2019 package [40].

169 **Cytotoxicity assay (XTT):** CHO-K1 cells were cultured in complete medium containing
170 DMEM+HAM F10 (1:1, v/v) (Sigma, St Louis, USA), 10 % fetal calf serum (Sigma, St Louis,
171 USA) and 1% of antibiotics penicillin/streptomycin stabilized solution (Sigma, St Louis, USA) in
172 cell culture flasks of 25 mm² (TPP, Switzerland). Cells were seeded in 6 (P1), 12 (P2), 24 (P3) or 48
173 (P4) cell plates with cell growth area of 9.5 cm², 3.8 cm², 1.9 cm² and 0.95 cm², respectively. After
174 24 h cell cultures were exposed to a polyurea piece (0,04 cm²) during 48 h, when cell viability was
175 assessed using the Cell Proliferation Assay Kit (Roche) according to manufacture instructions.
176 Percentage of viable cells was calculated considering the negative control as 100% viable after three
177 experimental repetitions. Differences between negative control and experimental groups were
178 evaluated using Analysis of Variance followed by Dunnet's test considering 95% of confidence.
179 Cell media and doxorubicine (1 µM) were used as negative control NC and positive control,
180 respectively.

181 **In vitro drug release assays:** temporal release of DCF was evaluated in distilled water (100

182 mL, pH 6) using ~ 0.3 g of loaded PolyU containing different amounts of DCF drug. The release
183 assays were carried out at a controlled temperature of 37 °C, under constant stirring (100 rpm). *In*
184 *vitro* studies were performed by UV-Vis spectroscopy, using a Cary60 dual-beam
185 spectrophotometer (Agilent Technologies) connected to an immersion probe (optical path length of
186 2 mm). Quantitative determination of the cumulative DCF release were performed using a
187 calibration curve constructed using the maximum absorbance values at $\lambda_{\text{max}}= 275$ nm of drug
188 solutions at different concentrations. All the *in vitro* cytotoxicity and release experiments were
189 performed with three independent samples, and the results are presented as data average.

190

191 3. Results and Discussion

192 3.1 Visual gel time

193 Gel formation from polyureas occurs as the condensation reaction proceeds. Several
194 parameters can affect the rate of this reaction. Indeed, amines are highly reactive in presence of
195 isocyanates, thus acetone was used to capping the amine groups of polyetheramine-PEO and to
196 evaluate the time of the gelation. **Figure 1** shows gelation time of the polyurea samples as a
197 function of contact time of PEO and HDI with acetone before their mixing (i.e. condensation
198 reactions). We observed that the contact time of the solutions (polyetheramine and HDI) with
199 acetone clearly reduces the reactivity of the polyether. Depending on their applications, e.g. coating
200 or spray processes, the combination of acetone solvent with fast gelation time is an important issue
201 to eliminate energy consuming baking ovens or dryers. **Figure 1** highlights the control over gel
202 time formation (from minutes to hours) by using acetone as solvent which decreases the reactivity
203 between amino groups (from polyether) with isocyanate. The contact time chosen for the rest of the
204 study (PolyU as carrier) was 90 min.

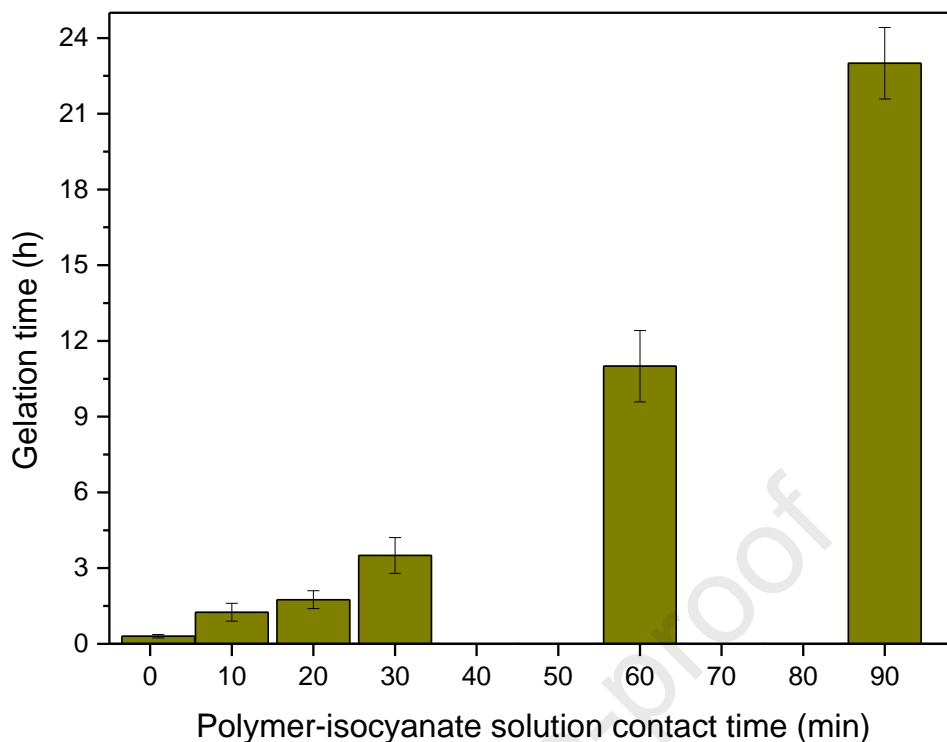


Figure 1

3.2 Structural characterization and theoretical studies

FTIR studies were performed to evaluate the possible interactions between polyurea matrix and DCF as a function of drug content (1-30 wt%). **Figure 2** shows the FTIR spectra of unloaded and loaded PolyU with the DCF drug from 1750 – 1400 cm^{-1} (**Figure 2a**) and 1300 – 700 cm^{-1} (**Figure 2b**). Regardless of the polyurea matrix (unloaded and loaded), the presence of bands centered at 1636 cm^{-1} (C=O amide I) and 1560 cm^{-1} (CO-N-H amide II) evidences the formation of urea groups (**Figure 2a**). It is important to note the absence of the peak at 2262 cm^{-1} (characteristic of the free isocyanate reactive group from HDI) and the presence of a band at $\sim 3346 \text{ cm}^{-1}$ (N-H ν , hydrogen-bond) [25] (see **Figure S2 for full FTIR spectra**). These results indicate the successful completion of the reaction between isocyanate and amino groups, after gelation process and curing at room temperature, and thus the formation of the polyurea network.

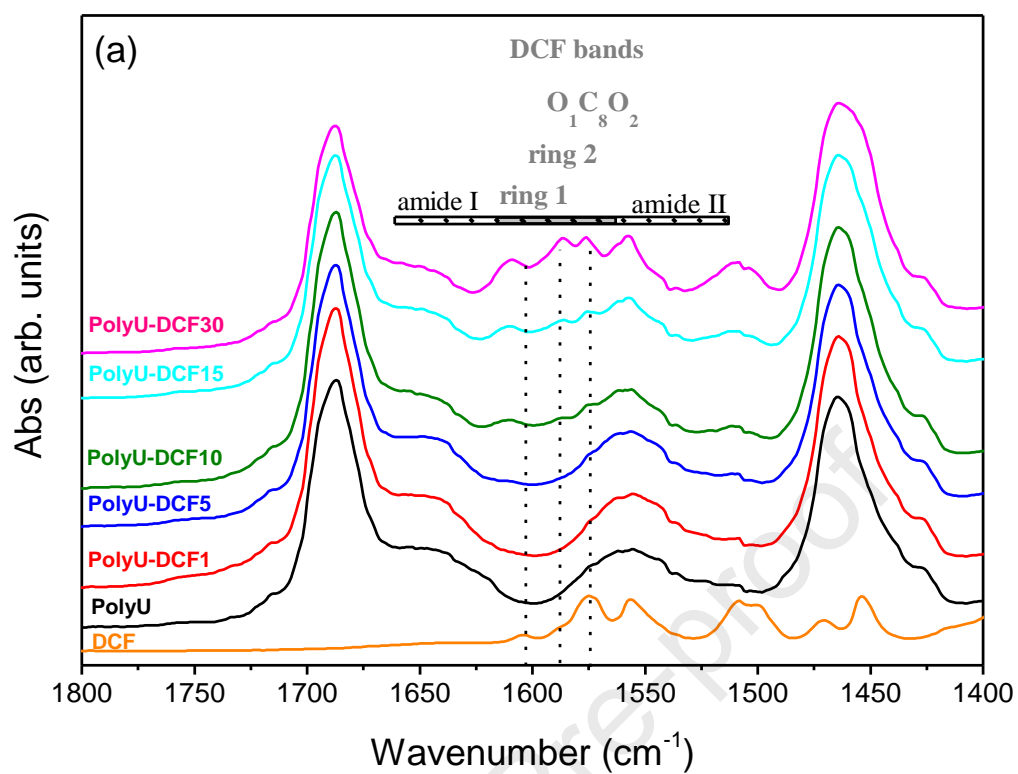
The polyether region (from 1300 – 700 cm^{-1} , **Figure 2b**) shows the characteristic bands at 1142, 1102, 948 and 846 cm^{-1} , attributed to the ethylene rocking vibrations (CH_2 r) and stretching

221 vibrations of the polyether PEO backbone ($C-O-C$ v) [26]. The FTIR spectrum of PolyU-DCF_x (x
222 = 1-10) closely resembles to the one of PolyU (**Figure 2a,b**): At low concentrations, the vibration
223 bands characteristic of DCF are not observed. As DCF content increases (15 and 30 wt%), bands
224 arise around 1576, 1586 and 1609 cm^{-1} , and are attributed to the $O_1C_8O_2$ asymmetric stretching
225 vibration, and the dichlorophenyl and phenylacetate rings stretching vibrations, respectively (**Figure**
226 **2a**). By comparing the spectrum of PolyU -DCF30 with the spectrum of DCF (illustrated in **Figure**
227 **S3a**) one can clearly see a shift of bands centered at 1605, 1589 and 1574 cm^{-1} , characteristic of the
228 DCF vibrations cited above. The polyether-PEO characteristic vibration bands do not show changes
229 in both frequency and peak position upon incorporation of the drug at any of the loaded amount
230 (**Figure 2b**). Furthermore, similar emerging and shift of the bands characteristic of DCF drug can
231 be noticed around 718, 749 and 780 cm^{-1} for the loaded polyurea samples with high DCF content
232 (15-30 wt%, see details **Figure 2b**, and **Figure S3b**). These results indicate the existence of
233 polyurea-DCF interactions that will be discussed below.

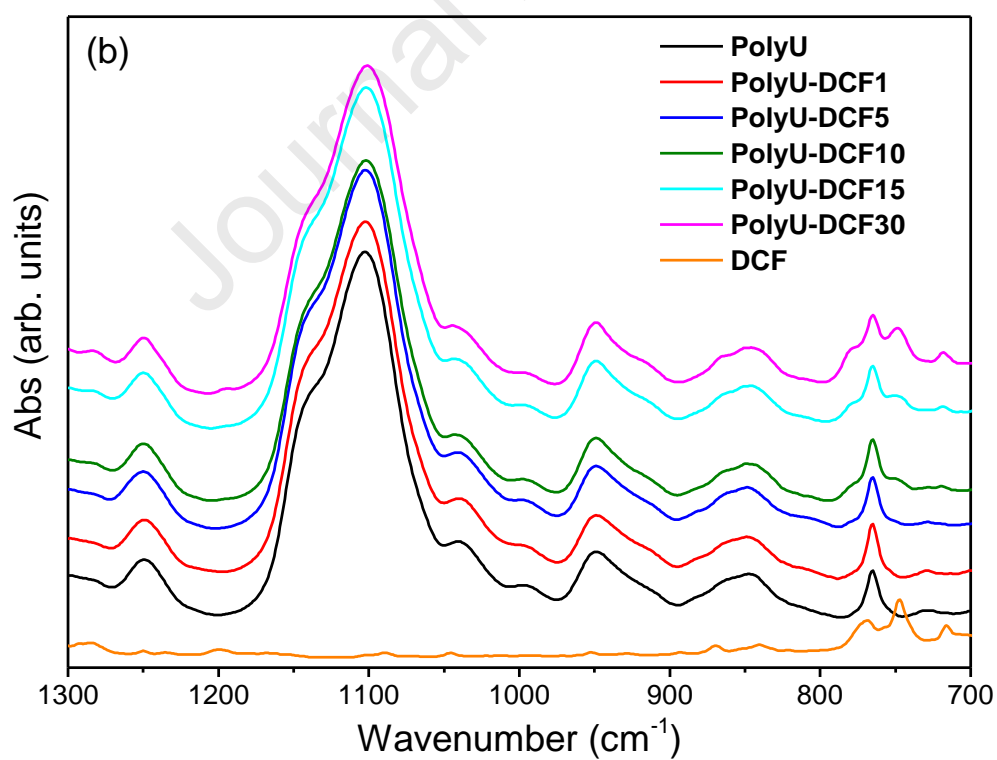
234

235

236



237

238
239

240

241

Figure 2

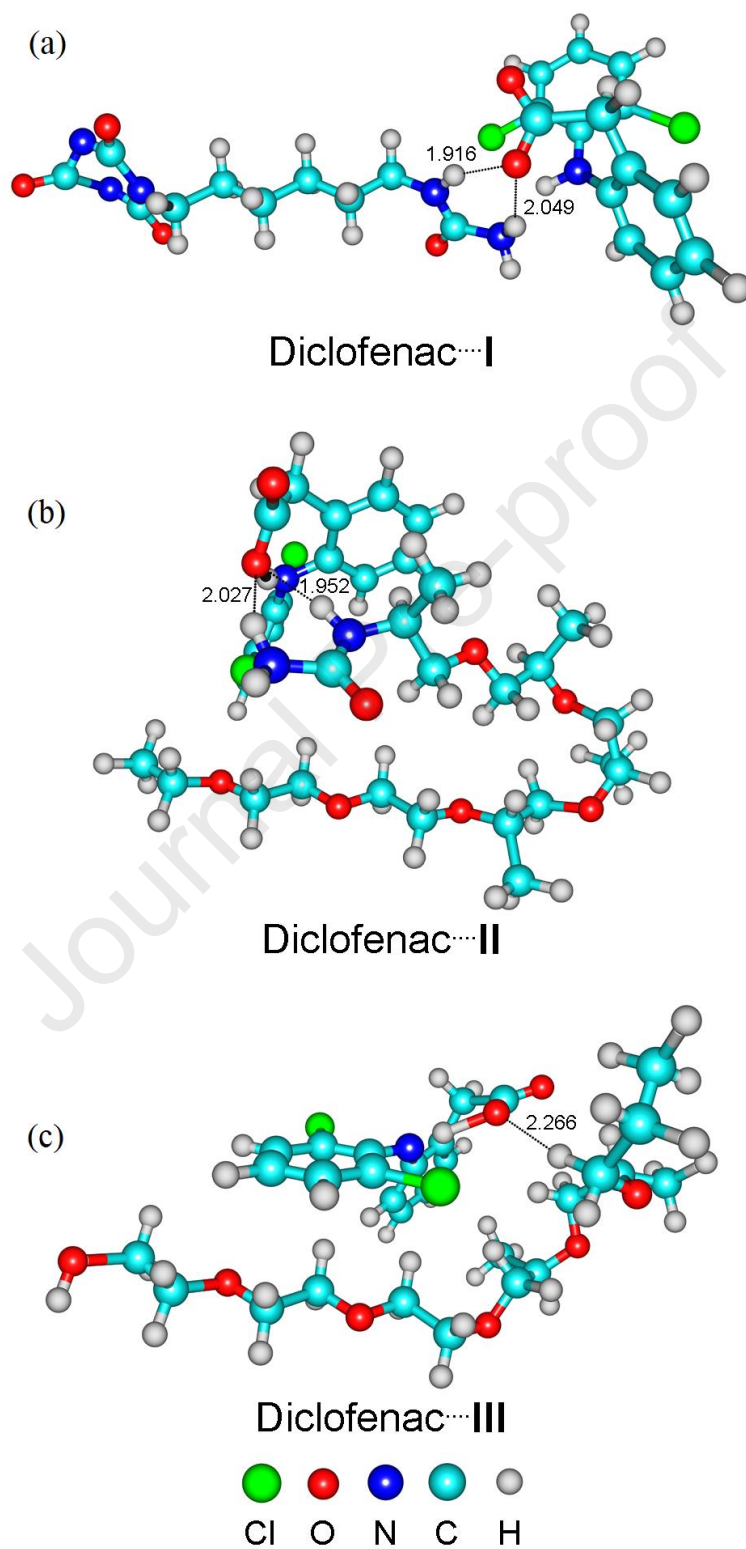
242

243 To evaluate the interactions between the DCF and the polyurea, we performed
244 computational studies using an energy decomposition analysis (EDA) looking at three
245 representative structures of the polymer network (See compounds **I–III** in **Figure S4**). The main
246 results are presented in **Table 1**. According to the EDA formalism [34], the interaction energy,
247 ΔE_{int} , is the summation of several terms corresponding to electrostatic, ΔV_{elstat} , Pauli repulsions,
248 ΔE_{Pauli} , orbital interactions, ΔE_{oi} , and dispersion ΔE_{disp} , components. The term ΔV_{elstat} represents the
249 quasi-classical electrostatic interaction between unperturbed charge densities and nuclei of the
250 geometrically deformed fragments. The Pauli-repulsion ΔE_{Pauli} contains the destabilizing
251 interactions between the occupied orbitals and is accountable for the steric repulsion. The orbital
252 interaction ΔE_{oi} reflects the charge transfer (donor-acceptor interactions between occupied orbitals
253 on one fragment with the empty orbitals of another fragment) and polarization
254 (unoccupied/occupied orbital mixing on one moiety due to the presence of the other). The term
255 ΔE_{disp} is the dispersion correction contributions [38].

256 **Figure 3** displays the form of interactions between the selected three polyurea derivatives (**I–**
257 **III**) and DCF drug. All interactions diclofenac \cdots (**I–III**) show an attractive nature due to negative
258 values of ΔE_{int} . In addition, these interactions are predominantly electrostatic due to the largest
259 contribution ($\sim 46\%$) of ΔV_{elstat} to the sum of all attractive energetic components $\Delta V_{\text{elstat}} + \Delta E_{\text{oi}} +$
260 ΔE_{disp} . However, it is important to highlight that in the DCF \cdots (**I** and **II**) complexes, there is also a
261 relevant contribution of the ΔE_{oi} component (41% and 26%) and a non-negligible role of the ΔE_{disp}
262 term (12% and 28%). The interactions diclofenac \cdots **III** are dispersion dominated, because of the
263 largest contribution of the ΔE_{disp} energy (43%) to the sum $\Delta V_{\text{elstat}} + \Delta E_{\text{oi}} + \Delta E_{\text{disp}}$. Nevertheless, the
264 diclofenac \cdots **III** interactions also show an important contribution of the ΔV_{elstat} term (34 %) and a
265 non-irrelevant weight of the ΔE_{oi} component (23 %) to $\Delta V_{\text{elstat}} + \Delta E_{\text{oi}} + \Delta E_{\text{disp}}$. Therefore, the
266 analysis of the interactions diclofenac \cdots (**I–III**) shows that the drug can establish favorable
267 interactions with the polymer in different bond sites. Furthermore, *in silico* studies suggest that the

268 major binding mechanisms involved hydrogen bonds, in particular between hydrogen atoms from
269 urea groups and diclofenac oxygen atoms.

270



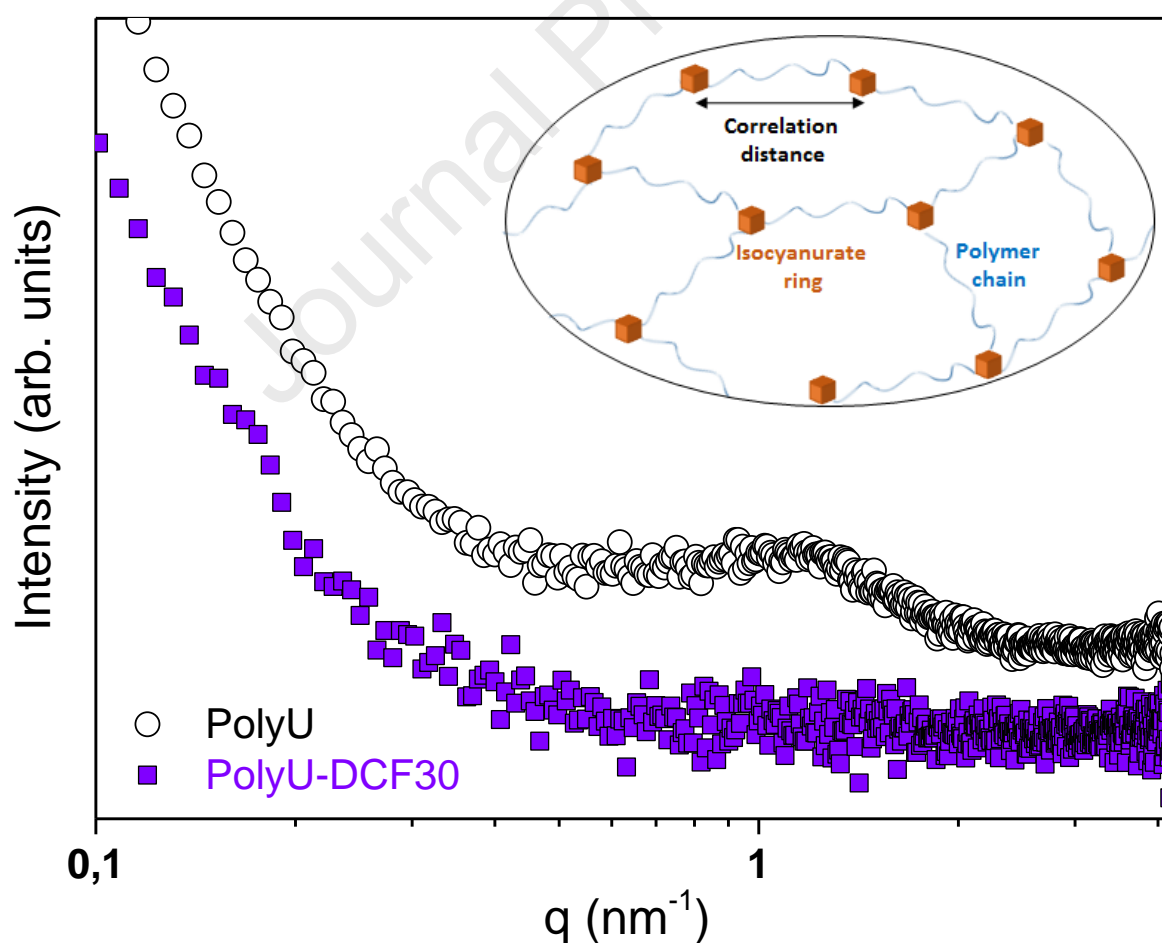
271

272

273

Figure 3

274 SAXS experiments were conducted to elucidate the microphase separation of the hard
275 domains embedded in the soft domains. **Figure 4** shows the SAXS diffractograms of PolyU and
276 PolyU-DCF30. The presence of a broad peak at $q = 1.15 \text{ nm}^{-1}$ for PolyU (black circles) is
277 characteristic of the average distance ($\xi = 54.6 \text{ \AA}$, calculated from $\xi = 2\pi/q_{\text{max}}$) between the hard
278 and soft domains [25,26]. The connection between triisocyanates groups (from isocyanurate rings of
279 HDI reagent) and polyetheramine-PEO generates microphase separation with distances as show in
280 the inset of **Figure 4**. This broad signal almost disappears upon incorporation of the drug (**Figure 4**,
281 **purple squares**) suggesting that the diclofenac molecules are coordinated to different bond sites
282 within the polymer (agreement with computational studies). This feature also strongly indicates that
283 the polyurea favors the high solubility of the drug within the polyether network. These results are in
284 line with thermal properties of polyurea as a function of drug amount loaded discussed below.



285

286

Figure 4

287 3.3 Thermal features

288 DSC experiments were conducted for evaluating the influence of DCF drug in both,
 289 amorphous phase (glass transition T_g) and semi-crystalline moieties of the polyurea network. All
 290 PolyU xerogels (unloaded and loaded with drug 1 – 30 wt%) showed a unique glass transition (T_g)
 291 and one melting temperature (T_m), **Figure 5a**. These two events (T_g and T_m) in DSC thermograms
 292 are characteristic of the polyether-PEO chain length and of the ethylene oxide moieties
 293 crystallization, respectively [41,42]. For PolyU (**Figure 5a black line**), T_g and T_m events were
 294 observed at approximately -58 °C and 21 °C, respectively. The great miscibility (solvation) of DCF
 295 within PolyU was confirmed by the existence of an unique T_g and the dependency of T_g values with
 296 the DCF content (**Figure 5a**). **Table 2** presents the glass transition and melting temperatures as well
 297 as the degree of crystallization (D_c) deduced from the DSC thermograms. The T_g was characterized
 298 by step changes in the heat capacity, and T_m can be obtained from the onset of the endothermic
 299 peak, while the crystallinity degree D_c (eqn (1)) is calculated using the ratio between the melting
 300 enthalpy of semi- crystalline PEO in the polyurea sample and the melting enthalpy of 100%
 301 crystalline PEO:

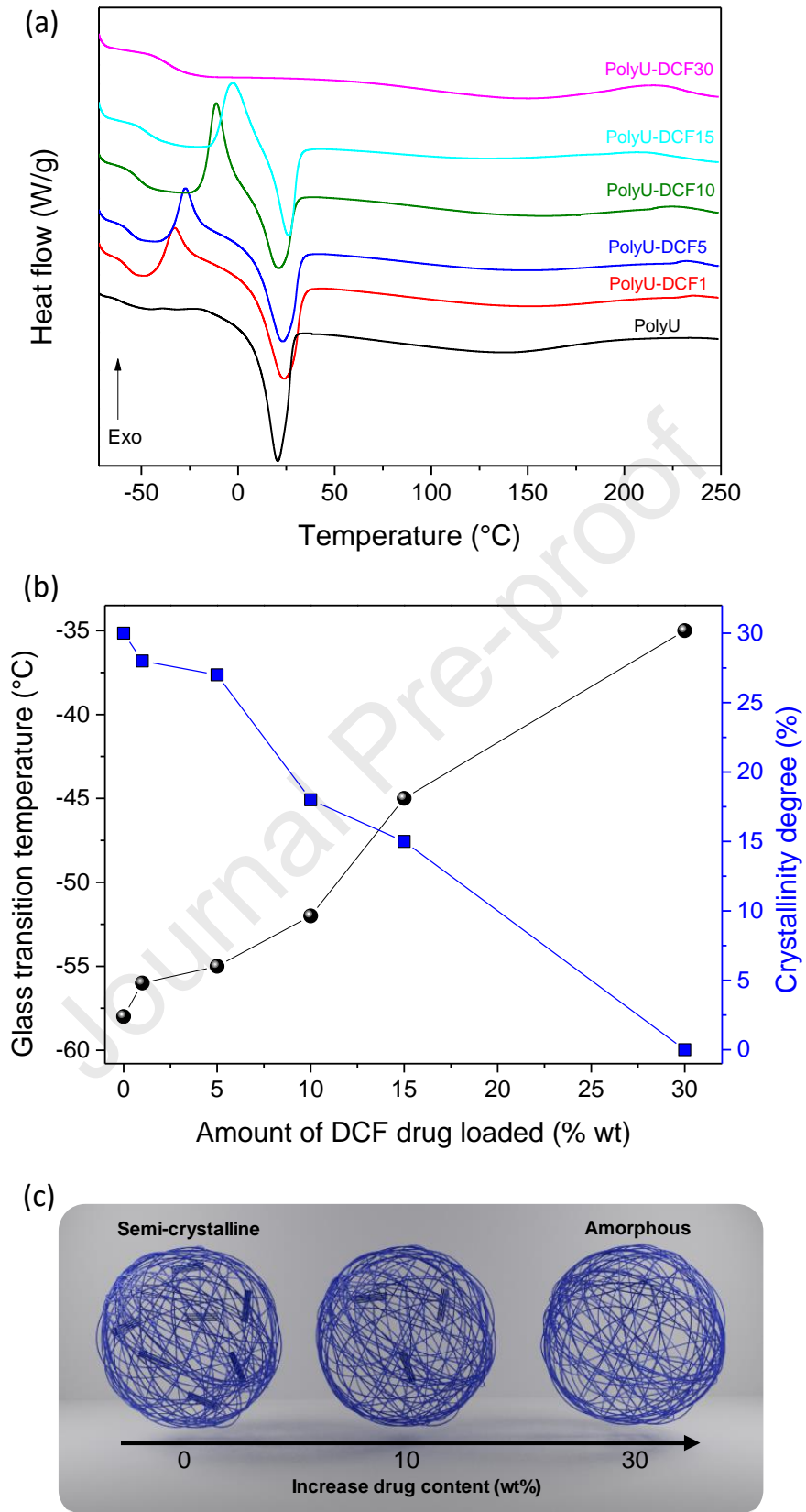
$$302 \quad D_c = \frac{\Delta H_m}{\Delta H_m^\circ} \times 100\% \quad (1)$$

303 where ΔH_m is the melting enthalpy per gram of PEO in the PolyU sample, and ΔH_m° is the
 304 melting enthalpy for 100% crystalline PEO (188.9 J g⁻¹) [43].

305 Upon DCF incorporation (1 – 30 wt%), significant changes are observed in the DSC
 306 thermograms and the T_g/T_m values (**Figure 5a, Table 2**). The presence of the drug through the
 307 polyurea network generates three main effects: (i) a significant increase in the glass transition T_g
 308 temperature from -58°C (PolyU) to -35°C (PolyU-DCF₃₀); (ii) a shift of the melting peak
 309 temperature centered at 21°C (PolyU) followed by a decrease of the crystallinity degree D_c and (iii)
 310 the appearance of a cold-crystallization characterized by an additional exothermic event between -
 311 50°C and 14°C. The linear and significant increase in T_g values (**Figure 5b**) and the decrease in the
 312 D_c , followed by a T_m shift (from 21°C to 29°C) as a function of the drug loading (see details in

313 **Table 2)** evidence the great solvation of DCF. Due to the presence of functional groups such as urea
314 and ether-type oxygen atoms (from polyether), high drug incorporation capability is achieved by the
315 polyurea network. These results are in good agreement with the theoretical and FTIR studies.
316 Furthermore, by incorporating a large amount of DCF (30 wt%) into PolyU, the coordination of the
317 drug through the semi-crystalline domains of PEO leads to a fully amorphous matrix (absence of
318 exothermic event characteristic of melting temperature of semi-crystalline phase, **Figure 5a, pink**
319 **line**). In this work, the inhibition of the PEO chains crystallization upon DCF coordination with
320 urea groups and polyether oxygens is an additional proof for the full solvation of DCF molecules.
321 In addition, the glass transition T_g values and crystallinity degree D_c (**Figure 5b**) show a linear
322 evolution with the increase of the DCF content, traducing an increase of the rigidity and a decrease
323 of the semi-crystalline domains amount, respectively. The inhibition of crystallization of the PEO
324 chains as a function of drug content is illustrated in **Figure 5c**. No crystallization of the PEO is
325 observed when a high amount of DCF drug is incorporated (**Figure 5a pink line and Figure 5c**
326 **illustration of PEO amorphous structure**), indicating a very rigid polyurea network with reduced
327 chain mobility (see T_g values in **Table 2**).

328



329

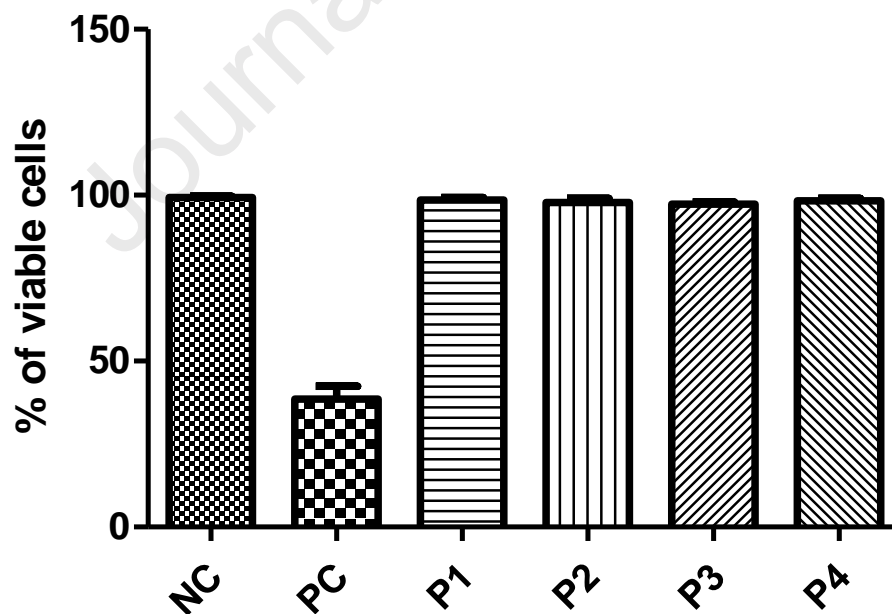
330

331

Figure 5

332 3.4 Citotoxicity evaluation

333 The evaluation of medical devices follows the International Organization for
334 Standardization (ISO) rules that recommend : “*in vitro* test methods, which are appropriately
335 validated, reasonably and practically available, reliable and reproducible shall be considered for use
336 in preference to *in vivo* tests” [44]. The polyurea sample was exposure to cells by direct contact
337 with culture medium according to ISO (2003) [45]. Thus, it mimics the physiological conditions by
338 a zone of diffusion in which could affects cellular trauma in accordance with the density of
339 materials [46,47]. According to **Figure 6**, no statistical differences were observed in terms of
340 citotoxicity between cells exposed to PolyU membrane and the negative control ($P>0.05$). The use
341 of cell plates with different cell growth area did not interfere in cell response to the presence of
342 PEO. Moreover, the CHO-K1 cells are recommended by the Organization for Economic Co-
343 operation and Development (OECD, 2016) for guideline applied to genotoxicity testing of
344 chemicals.

345
346
347 **Figure 6**
348
349

350 3.5 *In vitro* diclofenac release assays

351 The cumulative release of DCF incorporated into polyurea xerogel as a function of drug
352 loading (1 – 30 wt%) are shown in **Figure 7**. The release rate of DCF is low for polyurea samples
353 containing 1 and 5 wt% of DCF, with only a 13 and 36% release after 1440 min, respectively
354 (**Figure 7 red and blue squares**). For the polyurea matrices loaded with 10 – 30 wt% of DCF
355 (**Figure 7 green, cyan and purple squares**), the release rate was higher compared to samples with
356 lower amounts of drug incorporated (1 – 5 wt%).

357 The release rate of DCF may be described by simultaneous swelling front (water uptake)
358 and DCF release. To explain such a facile solvation (solubilization) of the drug through the polymer
359 backbone, we hypothesized interactions between PEO chains and diclofenac DCF. By increasing
360 the DCF amount loaded in polyurea xerogel a consequent augmentation of drug molecules present
361 on the surface (physisorbed) leads to a high cumulative release of the DCF until ~80% (**Figure 7**
362 **purple squares**). These results are in line with FTIR, theoretical, SAXS and DSC studies which
363 demonstrate i) interactions between DCF and the host matrix with the shift of the drug characteristic
364 bands in the FTIR spectrum, ii) favorable interactions with the polymer depending on the bonding
365 site, iii) evident decrease of the peak intensity in the SAXS pattern of the host and iv) clear changes
366 in glass transition temperature (T_g) followed by the inhibition of the polymer-PEO crystalline
367 moieties as a function of drug load. Here, the tuning of the cumulative release profiles (low or high
368 DCF amount released) have proven valuable in drug delivery applications, due to the ability to
369 easily encapsulate DCF molecules into polyurea by direct dissolving the drug in the PEO polymer.
370 Thus, this class of polyurea xerogel points out the precise control of DCF release by adjusting the
371 amount of drug loaded into polymer matrix.

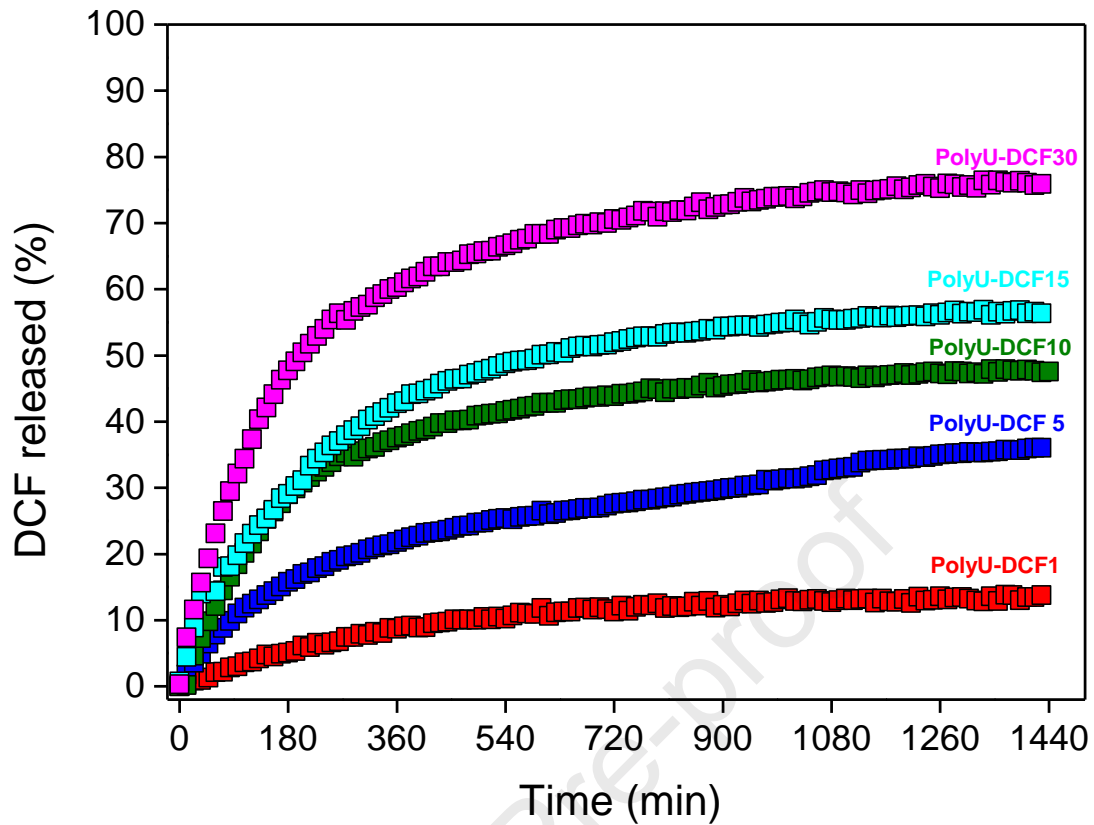


Figure 7

372

373

374

375

376

377

378

379

380

381

382

383

384

385

The release mechanism of the diclofenac from the loaded PolyU xerogel (1 – 30 wt%) was evaluated by Korsmeyer-Peppas equation [48] (eq. 2), where M_t is the solute mass released at time t , M_∞ is the initial solute mass, M_t/M_∞ is a fraction of the drug released at time t , k is the released rate constant and n is the released exponent which gives information regarding the drug transport mechanism [48]. Depending on the n value, different mechanisms can be envisioned: a Fickian diffusion (n value of ≤ 0.50), a case II transport indicated by a zero-order drug release (n value of ≥ 1), while an anomalous non-Fickian transport mechanism (swelling as well diffusion) is indicated by a n value of $0.50 < n < 1.0$.

$$\frac{M_t}{M_\infty} = k t^n \quad (2)$$

Figure 8 shows the release curves, plotted as $\log (M_t/M_\infty)$ vs. $\log t$, for loaded PolyU

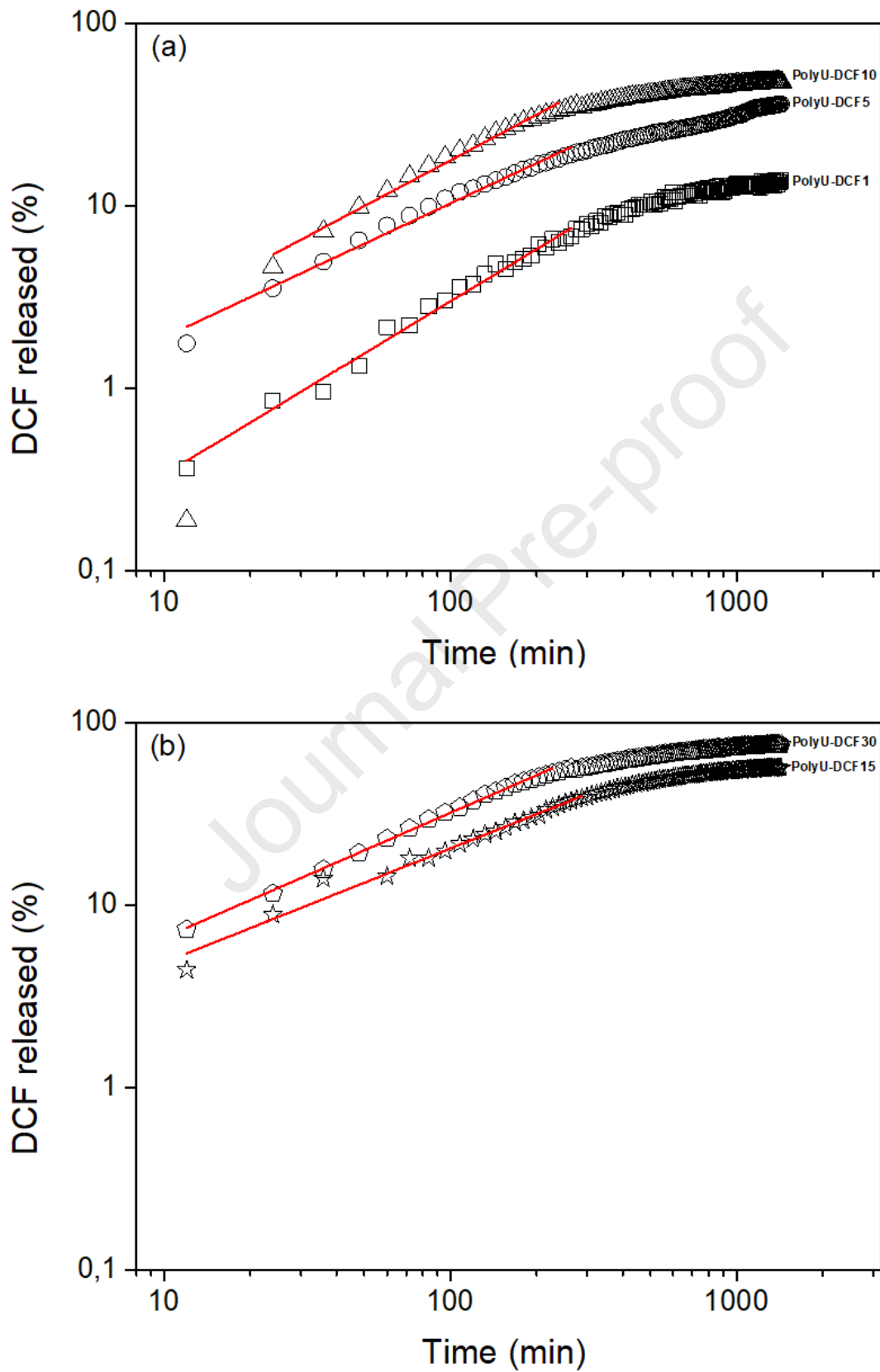
386 containing from 1 – 30 wt% of diclofenac. The kinetic curves of DCF loaded PolyU (1 – 30 wt %)
387 samples were well fitted with the Korsmeyer-Peppas model (one straight line - **Figure 8a,b**)
388 showing a coefficient of determination (R^2) for all samples of about 0.99. For the PolyU samples
389 containing between 5 and 30 wt% of diclofenac drug the experimental n values (see details in **Table**
390 **S3**) indicate an anomalous transport followed by diffusion/zero-order rate of drug controlled by the
391 penetration of the water-swollen front. For PolyU-DCF₁, the calculated n value being close to 1, it
392 suggests a Case II transport mechanism for which DCF drug release is mainly controlled by the
393 swelling effect of the polyurea matrix. The cumulative drug released by PolyU-DCF₁ sample,
394 suggests that the amount of DCF molecules available near the monolithic surface is low and that
395 entrapped DCF molecules begin to release by water uptake, at slow rate due to the DCF-PEO chains
396 interactions.

397 Recently, we demonstrated the possibility to incorporate simultaneously an anti-inflammatory
398 and an anticancer drug into a polyurea xerogel for dual delivery purposes [23]. A low loading of
399 amount of drugs (1 wt%) was used to evaluate the potential applications of polyurea as drug
400 delivery system. Herein, we highlight a facile and reproducible control over the amount of drug
401 encapsulated into polyurea xerogel in which 30 wt% of drug load can be easily reached and its
402 release profile can be modulated by the interactions with the host matrix. Moreover, the influence of
403 the drug amount loaded into structural/thermal polyurea properties was in depth correlated.

404 A cost estimation to produce polyurea PolyU using the synthesis conditions of this work was
405 evaluated. By using the identifiable components values at the laboratory scale prices to obtain three
406 polyurea membranes, the estimated cost (the summation of individual cost elements) was
407 approximately US\$ 2.00 (see **Table S4** and **Figure S5**). Due to their physico-chemical properties,
408 biocompatibility, easy-shaping, high capacity of drug loading, and low-cost production these
409 polyurea materials could be fabricated as contact lenses, films, microcapsules, bulky materials and
410 more, with broad implications for many fields. This work has clearly opened up highly interesting
411 prospects for the polyurea as biomaterials. Several aspects derived from the results reported here

412 need to be investigated in the future, such as *in vivo* assays.

413



414

415

Figure 8

416 **4. Conclusions**

417 A polyurea xerogel (PolyU) was synthesized by reaction between a polyetheramine (PEO)
418 and an aliphatic polyisocyanate (HDI). The PolyU matrix shows a high encapsulation capability of a
419 model drug diclofenac sodium (DCF) up to 30 wt%. Due to the sol-gel process, the simplicity of
420 industrial scale-up in the gel preparation at room temperature is also an important point favoring
421 their development as potential drug delivery vehicle. PolyU gel time formation could be controlled
422 (from minutes to hours) by the solvent contact time of the PEO and HDI before the condensation
423 reactions (mixture) between both reagents. We demonstrated novel insights into biological and
424 physical chemical properties of this class of polyurea xerogel containing DCF. In this sense, the
425 characterization of the materials shows a good correlation between the techniques used such as
426 FTIR, SAXS and DSC analysis. The existence of PolyU-DCF interactions (hydrogen bonds) was
427 confirmed by i) experimental FTIR/theoretical *in silico* results; ii) by SAXS with the disappearance
428 upon high DCF loading of the broad signal evidencing microphase separation and spatial
429 correlation between hard domains embedded in the polymeric matrix; iii) by thermal features
430 highlighting that the fraction of the crystalline polymer-PEO (endothermic fusion peaks in DSC
431 thermograms) was drastically affected as a function of DCF loading, indicating a stable compatible
432 mixture of the pair polyurea-drug leading to a complete amorphous polymeric nature and iv) by the
433 exposure of PolyU xerogel to CHO-K1 cells which shows a high cell viability suggesting that
434 polyurea matrix could be used as biomaterials. A precise control over DCF release was demonstrated
435 by the judicious choice of the drug loading amount into the PolyU matrix. The use of this class of
436 polyurea containing drugs open positive perspectives finding applications from drug delivery
437 systems like transdermal delivery patches, encapsulation for food formulation, beverages and
438 cosmetics.

439
440 **Conflicts of interest:** There are no conflicts to declare.

441
442 **Acknowledgements:** The authors would like to thank Celso V. Santilli and Rodrigo Santos for small angle
443 X ray scattering measurements (SAXS -EMU Instituto de Química - Câmpus de Araraquara), thank

444 Huntsman Performance Products and Bayer Group for donating the Jeffamine[®] and triisocyanate crosslinker
445 reagents, respectively. The authors are grateful to funding agencies CAPES (Finance Code 001), CNPq
446 (307696/2021-9), and FAPESP grant (n° 2021/06552-1 and SPRINT 2017/50286-9) and CNRS (PRC
447 Clustobrane).

448

449 **References**

- 450 [1] D. Moorkoth, K. M. Nampoothiri, S. Nagarajan, A. R. Girija, S. Balasubramaniyan, D. S.
451 Kumar, Star-Shaped Polylactide Dipyridamole Conjugated to 5-Fluorouracil and 4-
452 Piperidinopiperidine Nanocarriers for Bioimaging and Dual Drug Delivery in Cancer Cells, *ACS*
453 *Appl. Polym. Mater.* 3 (2021), 737-756.
- 454 [2] Y. Guo, Y. Li, S. Zhou, Q. Ye, X. Zan, Y. He, Y. Charged Poly(N-isopropylacrylamide)
455 Nanogels for the Stabilization of High Isoelectric Point Proteins, *ACS Biomater. Sci. Eng.* 7 (2021),
456 4282–4292.
- 457 [3] L. Xu, H. Wang, Z. Chu, L. Cai, H. Shi, C. Zhu, D. Pan, J. Pan, X. Fei, Y. Lei, Temperature-
458 Responsive Multilayer Films of Micelle-Based Composites for Controlled Release of a Third-
459 Generation EGFR Inhibitor, *ACS Appl. Polym. Mater.* 2 (2020), 741–750.
- 460 [4] H. Karimi-Maleh, S. J. Mousavi, M. Mahdavian, M. Khaleghi, S. Bordbar, M. L. Yola, R.
461 Darabi, M. Liu, Effects of silver nanoparticles added into polyurea coating on sulfate-reducing
462 bacteria activity and electrochemical properties; an environmental nano-biotechnology
463 investigation, *Environmental Research*, 198 (2021), 111251.
- 464 [5] K. Chang, Y. Liu, D. Hu, Q. Qi, D. Gao, Y. Wang, D. Li, X. Zhang, H. Zheng, Z. Sheng, Z.
465 Yuan, Highly Stable Conjugated Polymer Dots as Multifunctional Agents for Photoacoustic
466 Imaging-Guided Photothermal Therapy, *ACS Appl. Mater. Interfaces* 10 (2018), 7012–7021.
- 467 [6] D. Babikova, R. Kalinova, D. Momekova, I. Ugrinova, G. Momekov, I. Dimitrov,
468 Multifunctional Polymer Nanocarrier for Efficient Targeted Cellular and Subcellular Anticancer
469 Drug Delivery, *ACS Biomater. Sci. Eng.* 5 (2019), 2271–2283.
- 470 [7] M. Hamilton, S. Harrington, P. Dhar, L. Stehno-Bittel, Hyaluronic Acid Hydrogel Microspheres
471 for Slow Release Stem Cell Delivery, *ACS Biomater. Sci. Eng.* 7 (2021), 3754–3763.
- 472 [8] C. Cleeton, A. Keirouz, X. Chen, N. Radacsi, Electrospun Nanofibers for Drug Delivery and
473 Biosensing, *ACS Biomater. Sci. Eng.* 5, (2019), 4183–4205.
- 474 [9] W. Wang, M. Zhang, L. Chu, Functional Polymeric Microparticles Engineered from
475 Controllable Microfluidic Emulsions, *Acc. Chem. Res.* 47 (2014), 373–384.

- 476 [10] M. H. Jandaghian, H. Kazerooni, Performance of polyurea formulations against impact loads:
477 A molecular dynamics and mechanical simulation approach, *J. Appl. Polym. Sci.* 138 (2021),
478 50309.
- 479 [11] M. Soccio, R. Mazzoni, C. Lucarelli, S. Quattrosoldi, A. Cingolani, M. Fiorini, N. Lotti, T.
480 Tabanelli, Urea and Polyurea Production: An Innovative Solvent- and Catalyst-Free Approach
481 through Catechol Carbonate, *ACS Sustainable Chem. Eng.* 8 (2020), 15640-15650.
- 482 [12] Y. Zhang, Y. Wan, Y. Li, G. Pan, H. Yu, W. Du, H. Shi, C. Wu, Y. Liu, Thin-film composite
483 nanofiltration membrane based on polyurea for extreme pH condition, *J. Membr. Sci.* 635 (2021),
484 119472.
- 485 [13] N. Reed, N. U. Huynh, Rosenow, B.; Manlulu, K.; Youssef, G. Synthesis and characterization
486 of elastomeric polyurea foam, *J. Appl. Polym. Sci.* 137 (2020), 48839.
- 487 [14] D. Zhang, B. Li, X. Zhang, Z. Zhang, W. Wang, F. Liu, Phoxim Microcapsules Prepared with
488 Polyurea and Urea–Formaldehyde Resins Differ in Photostability and Insecticidal Activity, *J. Agric.*
489 *Food Chem.* 64 (2016), 2841–2846.
- 490 [15] G. Holden, N. R. Legge, R. Quirk, H. E. Schroeder, Thermoplastic Elastomers, 2nd ed.; Eds.;
491 Hanser/Gardner Publications: Cincinnati, OH, **1996**.
- 492 [16] A. Feula, A. Pethybridge, I. Giannakopoulos, X. Tang, A. Chippindale, C. R. Siviour, C. P.
493 Buckley, I. W. Hamley, W. A. Hayes, Thermoreversible Supramolecular Polyurethane with
494 Excellent Healing Ability at 45 °C, *Macromol.* 48 (2015), 6132–6141.
- 495 [17] R. E. Kieltyka, A. C. H. Pape, L. Albertazzi, Y. Nakano, M. M. C. Bastings, I. K. Voets, P. Y.
496 W. Dankers, E. W. Meijer, Mesoscale Modulation of Supramolecular Ureidopyrimidinone-Based
497 Poly(ethylene glycol) Transient Networks in Water, *J. Am. Chem. Soc.* 135 (2013), 11159–11164.
- 498 [18] E. Wisse, A. J. H. Spiering, P. Y. W. Dankers, B. Mezari, P. C. M. M. Magusin, E. W. Meijer,
499 Multicomponent Supramolecular Thermoplastic Elastomer with Peptide-Modified Nanofibers, *J.*
500 *Polym. Sci. A: Polym. Chem.* 49 (2011), 1764–1771.
- 501 [19] P. Paraskevopoulou, I. Smirnova, T. Athamneh, M. Papastergiou, D. Chriti, G. Mali, T.
502 Cendak, G. Raptopoulou, P. Gurikov, Polyurea-crosslinked biopolymer aerogel beads, *RSC Adv.*
503 10 (2020), 40843–40852.
- 504 [20] J. V. John, E. J. Seo, R. Augustine, I. H. Jang, D. K. Kim, Y. W. Kwon, J. H. Kim, I. Kim,
505 Phospholipid End-Capped Bioreducible Polyurea Micelles as a Potential Platform for Intracellular
506 Drug Delivery of Doxorubicin in Tumor Cells, *ACS Biomater. Sci. Eng.* 2 (2016), 1883–1893.
- 507 [21] C. Cuscó, J. Garcia, E. Nicolás, P. Rocas, J. Rocas, Multisensitive drug-loaded
508 polyurethane/polyurea nanocapsules with pH-synchronized shell cationization and redox-triggered
509 release, *Polym. Chem.*, 7 (2016), 6457-6466.

- 510 [22] K. R. Gajbhiye, B. P. Chaudhari, V. B. Pokharkar, A. Pawar, V. Gajbhiye, Stimuli-responsive
511 biodegradable polyurethane nano-constructs as a potential triggered drug delivery vehicle for cancer
512 therapy, *Int. J. Pharm.* 588 (2020), 119781.
- 513 [23] M. A. de Resende, G. A. Pedroza, L. H. G. M. C. Macêdo, R. de Oliveira, R.; M. Amela-
514 Cortes, Y. Molard, E. F. Molina, Design of polyurea networks containing anticancer and anti-
515 inflammatory drugs for dual drug delivery purposes. *J. Applied polymer Sci* 139, (2022), 51970.
- 516 [24] A. Sánchez-Ferrer, D. Rogez, P. Martinoty, Synthesis and Characterization of New Polyurea
517 Elastomers by Sol/Gel Chemistry, *Macromol. Chem. Phys.* 211 (2010), 1712–1721.
- 518 [25] A. Sánchez-Ferrer, V. Soprunyuk, M. Engelhardt, R. Stehle, H. A. Gilg, W. Schranz, K.
519 Richter, Polyurea Networks from Moisture-Cure, Reaction-Setting, Aliphatic Polyisocyanates with
520 Tunable Mechanical and Thermal Properties, *ACS Appl. Polym. Mater.* 3 (2021), 4070–4078.
- 521 [26] N. A. M. de Jesus, R. de Oliveira, M. Amela-Cortes, N. Dumait, S. Cordier, Y. Molard, E. F.
522 Molina, Facile and scalable design of light-emitting and ROS-generating hybrid materials made of
523 polyurea gels embedding a molybdenum cluster-based salt, *Dalton Trans.* 50 (2021), 8907–8916.
- 524 [27] A. D. Becke, Density-Functional Thermochemistry. V. Systematic Optimization of Exchange-
525 Correlation Functionals, *J. Chem. Phys.* 107 (1997), 8554–8560.
- 526 [28] S. Grimme, S. Ehrlich, L. Goerigk, Effect of the damping function in dispersion corrected
527 density functional theory, *J. Comp. Chem.* 32 (2011), 1456–1465.
- 528 [29] P. C. Hariharan, J. A. Pople, The influence of polarization functions on molecular orbital
529 hydrogenation energies, *Theoret. Chimica Acta* 28 (1973), 213–222.
- 530 [30] M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. de Frees, J. A.
531 Pople, Self-Consistent Molecular Orbital Methods. XXIII. A Polarization- Type Basis Set for
532 Second-Row Elements, *J. Chem. Phys.* 77 (1982), 3654–3665.
- 533 [31] M. J. Frisch, J. A. Pople, J. S. Binkley, Self-consistent molecular orbital methods 25.
534 Supplementary functions for Gaussian basis sets, *J. Chem. Phys.* 80 (1984), 3265–3269.
- 535 [32] E. F. Molina, R. L. T. Parreira, E. H. de Faria, H. W. P. de Carvalho, G. F. Caramori, D. F.
536 Coimbra, E. J. Nassar, K. J. Ciuffi, Ureasil-Poly(ethylene oxide) Hybrid Matrix for Selective
537 Adsorption and Separation of Dyes from Water, *Langmuir* 30 (2014), 3857–3868.
- 538 [33] K. A. Ford, Role of Electrostatic Potential in the in Silico Prediction of Molecular
539 Bioactivation and Mutagenesis, *Mol. Pharm.* 10 (2013), 1171–1182.
- 540 [34] Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A.
541 Robb, J. R. Cheeseman, G., Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato,
542 A. V. Marenich, J. Bloino, B. J. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz,
543 A. F. Izmaylov, J. L. Sonnenberg, D. Williams–Young, F. Ding, F. Lipparini, F. Egidi, J. Goings,
544 B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng,

- 545 W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y.
546 Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M.
547 J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi,
548 J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M.
549 Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas,
550 J. B. Foresman, D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.
- 551 [35] F. M. Bickelhaupt, E. J. Baerends, Kohn-Sham Density Functional Theory: Predicting and
552 Understanding Chemistry, *Rev. Comput. Chem.* 15 (2000), 1–86.
- 553 [36] A. D. Becke, Density-functional exchange-energy approximation with correct asymptotic
554 behavior, *Phys. Rev. A* 38 (1988), 3098–3100.
- 555 [37] C. Lee, W. Yang, R. G. Parr, Development of the Colle-Salvetti correlation-energy formula
556 into a functional of the electron density, *Phys. Rev. B* 37 (1988), 785–789.
- 557 [38] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, A consistent and accurate ab initio parametrization
558 of density functional dispersion correction (DFT-D) for the 94 elements H-Pu, *J. Chem. Phys.* 132
559 (2010), 154104.
- 560 [38] E. van Lenthe, E. J. Baerends, Optimized Slater-type basis sets for the elements 1–118, *J.*
561 *Comput. Chem.* 24 (2003), 1142–1156.
- 562 [39] C. F. Guerra, J. G. Snijders, G. T. Velde, E. J. Baerends, Towards an order-N DFT method,
563 *Theor. Chem. Acc.* 99 (1998), 391–403.
- 564 [40] E. F. Molina, S. H. Pulcinelli, V. Briois, C. V. Santilli, Fine-tuning of a nanostructure,
565 swelling, and drug delivery profile by blending ureasil–PEO and ureasil–PPO hybrids, *Polym.*
566 *Chem.* 5 (2014), 1897–1904.
- 567 [41] E. F. Molina, C. R. N. Jesus, L. A. Chiavacci, S. H. Pulcinelli, V. Briois, C. V. Santilli,
568 Ureasil–polyether hybrid blend with tuneable hydrophilic/hydrophobic features based on U-
569 PEO1900 and U-PPO400 mixtures, *J. Sol-Gel Sci. Technol.* 70 (2014), 317–328
- 570 [43] K. Y. Mya, K. P. Pramoda, C. B. He, Crystallization behavior of star-shaped poly(ethylene
571 oxide) with cubic silsesquioxane (CSSQ) core, *Polymer* 47, (2006), 5035–5043.
- 572 [44] ISO 10993-1 (2009). Biological evaluation of medical devices – Part 1: Evaluation and testing
573 within a risk management process. International Organization for Standardization, Geneva,
574 Switzerland.
- 575 [45] ISO 10993-1:2003. Biological evaluation of medical devices. Part 1: Evaluation and testing,
576 vol. 10993-1:2003.
- 577 [46] H. S. Baek, J. Y. Yoo, D. K. Rah, D. Han, D. H. Lee, O. Kwon, J. Park, Evaluation of the
578 extraction method for the cytotoxic testing of latex gloves, *Y. Med. J.* 46 (2005), 579-583.

579 [47] B. D. Ratner, S. J. Northup, Testing biomaterials, in: Ratner, B.D., Hoffman, A.S., Schoen,
580 F.J., Lemons, J.E. (Eds), Biomaterials science: an introduction to materials in medicine, Academic
581 Press, New York, **1996** pp. 215-220.

582 [48] R. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N. A. Peppas, Mechanisms of Solute Release
583 from Porous Hydrophilic Polymers, *Int. J. Pharm.* 15 (1983), 25–35.

584

585

586

Journal Pre-proof

587

588

Figure Legends

589 **Scheme 1.** Synthetic route for the preparation of polyurea matrix and schematic network showing
590 hard domains isocyanurate ring (yellow squares) and soft domains polyether chains (blue lines).

591

592 **Figure 1.** Gelation time formation of polyurea networks as a function of monomers contact time
593 with acetone solvent.

594

595 **Figure 2.** FTIR spectra of the unloaded and loaded polyurea PolyU containing different amount of
596 drug (1-30 wt%) in the region between (a) 1750 – 1400 cm^{-1} , and (b) 1300 - 7000 cm^{-1} .

597

598 **Figure 3:** Equilibrium geometries for the Diclofenac...(I–III) complexes [B97D3/6–31+G(2d,p)].
599 Distances are given in angstroms.

600

601 **Figure 4.** SAXS patterns of the unloaded PolyU and PolyU containing 30 wt% of drug DCF. Inset:
602 schematic representation of the microphases formed between the hard domains and soft domains in
603 the polyurea network and correlation distance between these domains.

604

605 **Figure 5.** (a) DSC thermograms of the unloaded and loaded PolyU containing different amount of
606 drug (1-30 wt%), (b) comparison of both T_g and T_m as a function of drug content, and (c) schematic
607 representation of the semi-crystalline PEO chains with decrease of crystallization degree induced by
608 the increase of diclofenac drug content.

609

610 **Figure 6.** Percentage of CHO-K1 viable cells obtained by XTT assay after 48 h exposure to PolyU
611 membrane (0.04 cm^2). The P1-P4 represents different well plates. NC: negative control (cell
612 media); PC: positive control (doxorubicin 1 μM).

613

614 **Figure 7.** Temporal evolution of cumulative amount released for polyurea PolyU containing
615 different amounts of diclofenac drug (1 – 30 wt%)

616

617 **Figure 8.** Plots of $\log(M_t/M_\infty)$ vs $\log t$ for release experiments of PolyU containing different
618 amounts of diclofenac drug (a) 1, 5 and 10 wt%; (b) 15 and 30 wt%.

619

620

621

622

623

TABLE

624

625 **Table 1.** Analysis of the bonding situation between the DCF drug and structures derived from
 626 polymer polyurea (**I–III**) through of the EDA method. The energy unit is kcal mol⁻¹.^[a,b]

627

Complex	ΔE_{int}	ΔV_{elstat}	ΔE_{Pauli}	ΔE_{oi}	ΔE_{disp}
Diclofenac··· I	-53.40	-39.92 (47)	30.88	-34.23 (41)	-10.12 (12)
Diclofenac··· II	-36.70	-34.01 (46)	37.05	-19.05 (26)	-20.70 (28)
Diclofenac··· III	-27.61	-19.64 (34)	29.97	-13.10 (23)	-24.83 (43)

628

^[a] $\Delta E_{\text{int}} = \Delta V_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{oi}} + \Delta E_{\text{disp}}$; ^[b] Values in parentheses correspond to the percentage of each stabilizing contribution

629

($\Delta V_{\text{elstat}} + \Delta E_{\text{oi}} + \Delta E_{\text{disp}} = 100\%$).

630

631

632

633

634

635 **Table 2.** Thermal characteristics determined by DSC measurements of the unloaded and loaded Pug
 636 containing different amount of DCF drug from 1 to 30 wt%.

637

Sample	T_g (°C)	T_m (°C)	D_c (%)
PolyU	-58	21	30
PolyU-DCF1	-56	23	28
PolyU-DCF5	-55	23	27
PolyU-DCF10	-52	21	18
PolyU-DCF15	-45	29	15
PolyU-DCF30	-35	-	-

638

639

640

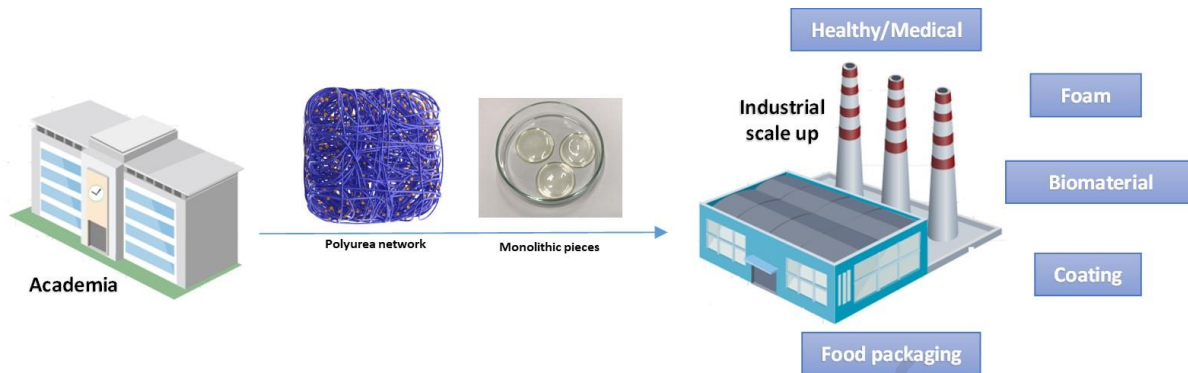
641

642

643

Graphical abstract

644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666



Highlights

Facile control over diclofenac drug release Kinects is described

Polyurea provide promising opportunities for scale up fabrication new functional devices

Versatile and cost-efficient carrier for drug delivery application

High amounts of anti-inflammatory drug loaded into polymer matrix

Journal Pre-proof

Cost-efficient Polyurea Carrier for Precise Control of an anti-inflammatory Drug Loading and Release

*Gabriele A. Pedroza,¹ Lucia H. G. M. C. Macedo,¹ Ricardo de Oliveira,¹ Natália S. Nascimento,¹ Renato P. Orenha,¹ Renato L. T. Parreira,¹ Raquel Santos,¹ Yann Molard,² Maria Amela-Cortes,² Eduardo F. Molina^{*1}*

¹Universidade de Franca, Av. Dr. Armando Salles Oliveira 201, 14404-600 Franca, SP, Brazil

²Université Rennes, CNRS, ISCR - UMR 6226, ScanMAT – UMS 2001, F-35000 Rennes, France

Credit author statement

G. A. Pedroza is the main author contributing in all steps. L. H. G. M. C. Macedo and R. de Oliveira performed gel time formation, drug delivery assays and FTIR measurements. N. S. Nascimento and R. Santos performed the cytotoxicity studies. R. L. T. Parreira and R. P. Orenha work on theoretical studies. Y. Molard and M. Amela-Cortes performed DSC analysis and worked on the results and discussion. E. F. Molina (supervisor of G. A. Pedroza) suggested the experiments, discussed the results and wrote the manuscript. All authors read and commented on the manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Journal Pre-proof