

1 **Design of pressure-sensitive adhesive suitable for the preparation of transdermal patches by**
2 **hot-melt printing**

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12 **Abstract:**

13 This work aimed to design low-melting pressure sensitive adhesives and demonstrate the feasibility
14 of the preparation of (trans)dermal patches by hot-melt ram extrusion printing. This approach allows
15 defining both the geometry of (trans)dermal patch and the drug strength easily according to patient
16 needs. The preparation steps are the mixing of a poly-ammonium methacrylate polymer (i.e. Eudragit
17 RL and RS) with a suitable amount of plasticizer (triacetin or tributyl citrate) and the drug (ketoprofen
18 or nicotine); the melting in the ram extruder and the printing on the backing layer foil. The
19 formulations were characterized in terms of rheological and adhesive properties, *in vitro* drug release
20 and skin permeation profiles.

21 The (trans)dermal patches made of Eudragit RL or Eudragit RS plasticized with the 40% triacetin
22 could be printed at 90°C giving formulations with suitable adhesive properties and which did not
23 exhibit cold flow after 1 month of storage at 40°C. Furthermore, the overall results showed that the
24 performances of printed (trans)dermal patches overlapped those made by solvent casting, suggesting
25 that the proposed solvent-free technology can be useful to treat cutaneous pathologies when the
26 availability of (trans)dermal patches with a size and a shape that perfectly fit with the skin area
27 affected by the disease improves the safety of the pharmacological treatment.

28

29 **Keywords**

30 Transdermal patches, Pressure-sensitive adhesive, Eudragit RL, Eudragit RS, Hot-melt extrusion,
31 Printing.

32

33 **1 Introduction**

34
35 (Trans)dermal patches are well-known pharmaceutical preparations designed to be applied onto the
36 skin surface for different purposes that range from the treatment of cutaneous pathologies to obtain a
37 systemic effect (Cilurzo et al., 2014a). Independently of the final goal, the basic design of a
38 (trans)dermal patch includes a backing layer, which protects the formulation from the outer
39 environment, an adhesive matrix, which contains the drug and controls its release, and a protective
40 foil, which is peeled out before the application of (trans)dermal patch (Wokovich et al., 2010).
41 Usually, the adhesive matrices are made of soft thermoplastic polymeric materials able to adhere on
42 the skin surface by simple contact under light pressure and to be peeled out without any residue. They
43 are defined as pressure-sensitive adhesives (PSA) and can be directly synthesized for this purpose or
44 compounded starting from pharmaceutical grade excipients (Cilurzo et al., 2008).
45 In particular, PSA used for the development of drug-loaded (trans)dermal patches by casting
46 techniques are available on the market or compounded as water or organic solvent dispersions
47 (Cilurzo et al., 2014b). Alternatively, hot-melt technologies could be applied since they allow a
48 cheaper production of (trans)dermal patches (Wilson et al., 2012). Usually, the basic approach to
49 produce a hot-melt PSA consists in the preparation of a blend in the hot mixer, in the transfer of the
50 obtained PSA in suitable containers and its cooling. Afterwards, the required PSA amount is
51 deposited in a heating container and, when melted, pumped onto the coater unit, which laminates the
52 PSA on the release liner at the desired thickness. This approach is widely used in the production of
53 medical devices, but it has been scantily investigated in the pharmaceutical field even if hot melt PSA
54 could open new opportunities from both a formulation and preparation point of view. Then, the PSA
55 laminated is associated with backing layer and cut to obtain the final shape and size of the
56 (trans)dermal patch. Both hot-melt extrusion and solvent casting are semi-continuous manufacturing
57 processes and, therefore, unsuitable either for scaling down the batch size or the personalization of
58 the dose.

59 Consequently, when the market shares of a (trans)dermal patch are too low to ensure the economic
60 sustainability of the manufacturing process, the access to therapies is jeopardized. In this case, the
61 availability of a system suitable for the preparation of very small batches could be useful for the
62 specific patient need. As an example, the production of scopolamine transdermal patches, which had
63 been indicated for the treatment of motion sickness, was interrupted in the last years. This decision
64 of the manufacturer has a substantial impact on patients affected by amyotrophic lateral sclerosis,
65 who used the scopolamine transdermal patches as off-label treatment for managing the sialorrhea
66 (Garuti et al., 2019).

67 The conventional 3D printing technologies cannot be applied to the preparation of (trans)dermal
68 patches, since the pressure-sensitive adhesives are very soft and sticky and cannot be used for the
69 production of pre-made filaments such those used for fused-deposition modelling (FDM) 3D printing.
70 Only a few pieces of evidence on self-adhesive nanofiber networks have been reported (Shi et al.,
71 2014).

72 This work explores the possibility to print of very small batch of (trans)dermal patches compatible
73 with the extemporaneous preparation for specific patients. To demonstrate the feasibility of such a
74 process we investigated the critical aspects related to the application of printing a melted PSA with a
75 specific geometry on the backing layer of (trans)dermal patch. PSA made of Eudragit RL or RS,
76 suitably plasticized by triacetin (TRI) or tributyl citrate (TBC), were used. These materials were
77 selected since it was already demonstrated that the rheological properties of highly plasticized
78 Eudragit RL are suitable for the preparation of PSA (Quaroni et al., 2018). Indeed, during the bonding
79 phase (tack), these materials behave like a viscous liquid to favour its spreading onto the skin and to
80 form good molecular contact under a lightly applied pressure. Conversely, during the debonding
81 process from the skin (peel), the adhesive should behave like a cohesive solid to ensure complete
82 removal without leaving any residue (O'Connor and Willenbacher, 2004). Furthermore, a
83 (trans)dermal patch should remain attached to the skin for the entire treatment period, without any
84 overspreading of the adhesive matrix beyond the boundaries. Therefore, it should also be highly

85 dissipative and lightly physically or chemically crosslinked to resist the applied stress once the bond
86 is formed.

87 Keeping in mind these features, the formulation space was investigated by using different
88 copolymers' ratio blended with different amounts of the selected plasticizers and their impact on the
89 adhesive properties of (trans)dermal patch was also checked. Then, the suitability of the selected PSA
90 for the preparation of (trans)dermal patches was tested by loading ketoprofen (KP) and nicotine (NT)
91 and comparing their performances with those of analogous (trans)dermal patches prepared by casting
92 (Quaroni et al., 2018).

93 The printing was performed according to a protocol already described for the preparation of
94 orodispersible films (Musazzi et al., 2018b). Briefly, the preparation procedure is simple and consists
95 in wetting the powders (i.e. the drug and the copolymer) with the plasticizer, loading the mixture in
96 the printer and printing the melt directly on the backing layer. Afterwards, the (trans)dermal patches
97 were coupled with the release liner and sealed in an airtight bag.

98

99 **2 Materials and methods**

100

101 **2.1 Materials**

102 Poly-(ethylacrylate-co-methylmethacrylate-co-trimethylammonioethylmethacrylate chloride), trade
103 with the name Eudragit® RL PO (EuRL) and Eudragit® RS PO (EuRS), with a molar ratio of 1:2:0.2
104 and 1:2:0.1 respectively, were kindly donated by Rofarma Italia (I). Tributyl citrate (TBC) was
105 supplied by Morflex (US), whereas triacetin (TRI) and NT were purchased from Sigma Aldrich
106 (Milan, I). KP was purchased from Farmalabor (I). The release liner and the backing layers tested
107 were kindly donated by Bouty S.p.A. (I). All solvents were of analytical grade unless specified.

108

109 **2.2 Preparation of (trans)dermal patch**

110 The mixtures were obtained by mixing the accurately weighted amount of each component in a mortar
111 according to the composition reported in **Table 1** and **Table 2**. The final weight of each mixture was
112 about 10 g.

113 The mixture was immediately transferred in the ram extrusion apparatus previously described
114 (Musazzi et al., 2018b), melted and printed at 90°C through a 0.7-mm needle. The printer was
115 designed modifying a Cartesian FDM 3D printer (Futura Group Srl, Italy), substituting the FDM
116 apparatus with a home-made ram extrusion system. The distance from the needle tip to the surface of
117 the backing layer was fixed at 0.3 mm to permit a suitable deposition of the melted blend, in a unique
118 layer, and to obtain an adhesive matrix with a thickness around 50-70 µm. The speeds of the mobile
119 plate and the extruder ram were set at 12 mm/s and 10 mm/s, respectively. Finally, the filling angle
120 was set at 135° to the X-axis of the baking layer.

121 The melted materials extruded through the die was deposited on the 20 × 20 cm backing layer foil
122 fixed in the Cartesian plate of the printer. The dimension and number of (trans)dermal patches per
123 each print were set up by 3D builder® (Microsoft, US) and converted in G-code. Afterwards, the
124 (trans)dermal patches were matched with a siliconized polyethylene film sealed in the primary
125 packaging and stored until use without further manipulations.

126

127 **2.3 Rheological tests**

128 The polymeric blends were prepared according to the procedure reported above. The sample was
129 printed on a release liner having both the surface coated with a different layer of silicon and then
130 covered with the same material. Afterwards, the sandwich was pressed to smooth the surface. The
131 rheological properties of the formulations were assessed and reported in **Table 1**. The assays were
132 conducted at $21 \pm 0.2^\circ\text{C}$ using a Physica MCR 302 rheometer (Anton Paar GmbH, A) with a cone-
133 plate geometry of 1° incline, 50 mm diameter. Minimum plate gap was set at 100 µm. Before the

134 analyses, a strain test was performed to determine the linear viscoelastic range of the samples: after
135 the test, shear strain for the experiments was set at 5%.

136 Frequency sweep experiments were performed, going from 0.01 rad/s to 100 rad/s, collecting 16
137 points in the range chosen, with logarithmic progression. The data were analysed as previously
138 described (Quaroni et. al, 2018). The complex viscosity (η^*) determined at 1.5 Hz, and the crossover
139 of G'/G'' were determined as descriptors of the rheological pattern of the prepared PSA. In particular,
140 the η^* , calculated according to the Eq. 1, was used to predict the steady shear viscosity according to
141 the Cox-Merz rule, which states that the complex viscosity as a function of frequency is equivalent
142 to the steady shear viscosity as a function of shear rate (Hicks et al. 2015):

$$143 \quad \eta^* = \frac{G^*}{\omega} \quad (1)$$

144 where G^* is the complex modulus at the established angular frequency (ω).

145

146 **2.4 Thickness of (trans)dermal patch**

147 The film thickness was measured by using a micrometer MI 1000 μm (ChemInstruments, US). The
148 results were expressed as the mean \pm standard deviation of five specimens for each formulation.

149

150 **2.5 Optical microscopy**

151 The overall morphology, the appearance of the printed patches (including crystal formation) were
152 evaluated by optical microscopy with a stereomicroscope (Nikon, I). Micrographs were acquired at
153 $10\times$ magnification with a digital camera of 3.1 Mpx (CCD 3, ToupView, ToupTek, China).

154

155 **2.6 Adhesive properties determination**

156 The adhesive and cohesive properties of the printed (trans)dermal patches were tested applying
157 standard procedures generally used for the characterization of (trans)dermal patches: cold flow, probe
158 tack test, shear adhesion test and peel adhesion 180° test (Cilurzo et al., 2012; Quaroni et al., 2018).

159 *Cold flow* – The cold flow is one of the possible quality defects of (trans)dermal patches and
160 represents the migration of a PSA outside the edge of the backing layer during the storage. This
161 phenomenon can be observed when the matrix of (trans)dermal patch has a significant viscous-like
162 behaviour to flow between the backing layer and release liner. The cold flow was evaluated on
163 samples of 25 x 50 mm after a storage period of 1 month at room temperature (RT) or $40 \pm 1^\circ\text{C}$. The
164 sample complied with the test when the PSA was not visually detectable outside the backing layer.
165 When occurring, the extent of cold flow was expressed as the maximum migration of the adhesive in
166 millimetre on the release liner. It was measured putting the sample, which was in any case almost
167 transparent, on a graph paper.

168 The analysis was performed in triplicate. If the cold flow was observed, the formulation was
169 discarded.

170

171 *Probe tack test* – The tack adhesion test reveals the force of debonding the PSA matrix from a surface
172 after a short contact time and applying light pressure. It is relevant for (trans)dermal patch since it
173 allows to estimate the initial bonding of a PSA onto the application site. Briefly, (trans)dermal patches
174 of 25 x 60 mm were printed from each formulation and stored at $25 \pm 1^\circ\text{C}$ for two weeks to assure
175 the stabilization of the adhesive matrix (Quaroni et al., 2018). The probe tack test was performed
176 according to a standard internal procedure using a tensile testing machine equipped with a 50 N cell
177 (Instron 5965, ITW Test and Measurement Italia S.r.l., I). A strip of double-coated tape (TESA, D)
178 having the same size of the plaster specimen was applied between the flat bottom plate of the tensile
179 testing machine and the backing layer of the specimen. The release liner of (trans)dermal patch was
180 then removed. The flat stainless-steel probe (diameter: 5 mm) was placed ~ 0.05 mm above the
181 adhesive matrix. The probe was then lowered onto the adhesive surface, and a constant force of 0.05 N
182 was applied onto the sample for 5 s and, finally, the probe was removed at the debonding rate of
183 0.1 mm/s. The absence of PSA residues on the probe surface (adhesive failure) was visually
184 determined. The whole force-distance curve (compression and traction) was recorded. The area under

185 the curve force vs probe displacement was assumed as the work of separation (W). The tack stress
186 (σ_{\max}) values for each experiment were calculated as the maximum traction force normalized by the
187 probe area. The results were expressed as the mean \pm standard deviation of four determinations.

188

189 *Shear adhesion test* – The shear adhesion test reveals the resistance of a PSA matrix to tangential
190 stress and, therefore, the cohesion of the matrix of (trans)dermal patch. Briefly, specimens of 25 x 60
191 mm were printed from each formulation (**Table 1** and **2**) and stored at $25 \pm 1^\circ\text{C}$ for two weeks to
192 assure the stabilization of the adhesive matrix (Quaroni et al., 2018). The shear adhesion was
193 performed using an 8 Bank Oven Shear HT8 Instrument (ChemInstruments, Ichemico, I) according
194 to a method previously described using a 500 g mass to generate the stress. The experiments were
195 performed at room temperature ($25 \pm 1^\circ\text{C}$). The results were expressed as the mean \pm standard
196 deviation of four specimens.

197

198 *Peel adhesion 180° test* – The peel adhesion reveals the resistance of (trans)dermal patch to peeling-
199 off. It has a crucial role in the characterization of (trans)dermal patch since high peel adhesion resulted
200 in a more painful its removal from the skin by the patient. The tests were performed using a tensile
201 machine equipped with a 50 N cell (Instron 5965, ITW Test and Measurement Italia S.r.l., I) using a
202 Teflon® panel, accordingly to the method described by Cilurzo and co-workers (Cilurzo et al., 2008).
203 (Trans)dermal patches printed with a 12 x 80 mm size were stored in primary packaging material at
204 $25 \pm 1^\circ\text{C}$ for two weeks before use.

205

206 **2.7 Drug content**

207 An accurately weighed 2.54 cm^2 (trans)dermal patch was dissolved in 50 mL methanol by
208 mechanically shaking and sonication (UP200st, Hielscher, D). Afterwards, the samples were left to
209 rest overnight and, then, diluted 1:1 with mobile phase described below. Before the injection, samples
210 were filtered with a $0.45\ \mu\text{m}$ polypropylene filter (VWR International, I). The drug content in the

211 (trans)dermal patch was calculated as a function of both the matrix mass ($\mu\text{g/g}$) and area ($\mu\text{g}/\text{cm}^2$).
212 The results were expressed as the mean \pm standard deviation of three specimens for each formulation.

213

214 **2.8 In vitro dissolution test**

215 The dissolution was performed by using an apparatus SR8 PLUS dissolution test station (Hanson
216 Research, US) according to the disk assembly method described in the “Dissolution test for
217 transdermal patches (01/2008:20904)” of European Pharmacopoeia.

218 An 8.0 cm^2 (trans)dermal patch was placed flat on the iron disk (mesh size of the disk net: $125\ \mu\text{m}$)
219 with the adhesive surface facing up according to the method previously described. The vessels were
220 filled with 300 mL of pH 7.4 PBS buffer, the water bath temperature was kept at $32.0 \pm 0.5\ ^\circ\text{C}$, and
221 the paddle speed was set at 25 rpm. At predetermined intervals (5, 10, 20, 30 min, 1, 2, 4, 6, 7, 24 h),
222 5 mL samples were collected and immediately replenished with fresh medium.

223 The solutions were assayed by HPLC, according to the methods reported below. The results were
224 expressed as the mean \pm standard deviation of three specimens for each formulation. The release rate
225 constant was calculated according to Higuchi's equation as follows:

$$226 \quad M_t/M_\infty = Kt^{0.5} \quad (2)$$

227 where M_t is the amount of drug released at time t , M_∞ is the drug loading in the matrix and K is the
228 release rate constant expressed as h^{-1} .

229

230 **2.9 In vitro permeation studies**

231 The permeation studies were performed using abdominal skin from donors, who underwent cosmetic
232 surgery. According to an internal protocol (Casiraghi et al., 2016), after removing the subcutaneous
233 fatty tissue, the skin samples were immersed in water at $60\ ^\circ\text{C}$ for 1 min, and the epidermis was
234 carefully removed from the underlying tissue with the help of forceps. The integrity of epidermis
235 samples was assessed measuring their electrical resistance (voltage: 100 mV, frequency: 100 Hz;
236 Agilent 4263B LCR Meter, Microlease, I), using a modified Franz diffusion cell (PermeGear, US)

237 with an effective permeation area and a receptor volume of 0.636 cm² and 3 mL, respectively.
238 Samples with an electrical resistance higher than 20 kΩ·cm² were used for the *in vitro* permeation
239 experiments (Cilurzo et al., 2018).

240 At the beginning of the *in vitro* permeation studies, a 2.5 cm² circular sample, obtained from a printed
241 (trans)dermal patch by a precision die cutter, was gently applied to the epidermis specimen. Then, the
242 assembly was mounted on the receiver compartment of the Franz diffusion cell filled with saline
243 solution, containing sodium azide (100 µg/mL), as a preservative, and maintained at 35 ± 1 °C, so
244 that the skin surface temperature was 32 ± 1 °C. Special care was taken to avoid air bubbles between
245 the epidermis and the medium in the receptor compartment. The receptor medium was continuously
246 stirred with a small magnetic bar at 1800 rpm to assure a uniform distribution of the permeated drug.
247 The upper and lower parts of the Franz diffusion cell were sealed with Teflon (VWR International, I)
248 and Parafilm® (Pechiney Plastic Packaging Company, US) and fastened together using a clamp. At
249 predetermined times (1, 3, 5, 7, 24 h), 200 µL samples were withdrawn from the receiver compartment
250 and replaced with fresh receiver medium. Sink conditions were maintained throughout the
251 experiments. Samples were analysed by HPLC according to the methods described below. The
252 cumulative amount (Q) permeated through the skin per unit of area was calculated from the
253 concentration of each substance in the receiving medium and plotted as a function of time. The steady
254 flux (J) was calculated as the slope of the linear portion of the plot.

255

256 **2.10 HPLC method**

257 The drug content and the drug concentration in the dissolution medium were quantified by HPLC
258 analysis (Agilent HP 1100, Chemstation, Hewlett Packard, US), using the following analytical
259 methods.

260 *Ketoprofen* – the following chromatographic conditions were used: column, HyperClone™ 5 µm
261 BDS C18 130, 150x4.6 mm (Phenomenex, US); mobile phase, acetonitrile/water pH 2.6 (60/40, %
262 v/v); flow rate, 1.5 mL/min; wavelengths, 225 nm; temperature, 25 °C; injection volume, 20µL. The

263 drug concentrations were determined from standard curves in the 0.1–50.0 µg/mL range ($R^2 =$
264 0.99999).

265 *Nicotine* – the following chromatographic conditions were used: column, Lichropher 110RP-18E,
266 125x4.0 mm, 5 µm (CPS Analytica, I) mobile phase, acetonitrile/ KH_2PO_4 0.1M solution (25/75, %
267 v/v) + 1.3 g/L sodium dodecyl sulphate; flow rate, 1.5 mL/min; wavelengths, 245 nm; temperature,
268 30 °C; injection volume, 20 µL. The drug concentrations were determined from standard curves in
269 the 0.1–50.0 µg/mL range ($R^2 = 0.99992$).

270

271 **3 Results and Discussion**

272

273 **3.1 Rheological pattern of designed formulations**

274 Rheological analyses show common trends according to the formulation tested: as expected,
275 increasing the plasticizer ratio, the viscosity gets lower with both TBC and TRI. **Fig. 1** shows the
276 typical pattern of rheological analyses. As a general statement, EuRL formulations had higher
277 viscosities in comparison to EuRS ones. This finding is probably due to a higher concentration of
278 quaternary ammonium salt in EuRL, which increases ionic content and, consequently, the interactions
279 with the polar groups of the plasticizer. A considerable difference between EuRL and EuRS is visible
280 checking the crossover values, i.e. the frequency corresponding to the equivalence between loss (G'')
281 and storage (G') modulus (**Table 1**). Accordingly, crossover occurs at higher frequencies when EuRS
282 is used in comparison to the same formulations containing EuRL (**Table 1**), indicating that elastic
283 modulus retains higher values for a higher range of frequencies. This different pattern confirmed the
284 role of the percentages of ammonium groups present in the two copolymers. Interestingly, when using
285 a 60/40 polymer/plasticizer ratio, a double crossover can be seen or expected, with the second
286 crossover close to the highest frequency used for the analysis (100 rad/s).

287 The values of $\tan \delta$ (i.e. the G''/G' ratio) minimum agree with the trends of G'' vs G' , i.e. when EuRL
288 and TBC are present, $\tan \delta$ minimum is visible at lower frequencies. When higher amounts of
289 plasticizer are used, the minimum is out of the frequency range used for the analyses.

290

291 **3.2 Selection of the pressure-sensitive adhesive composition**

292 In agreement with the results of rheological analyses on polymeric blends, both the type of copolymer
293 (i.e., EuRL or EuRS) and plasticizer (i.e., TBC or TRI) significantly impacted on the printability of
294 the placebo (trans)dermal patches (**Table 1**). In particular, for EuRS, the use of both plasticizers in
295 concentrations equal to 60% w/w resulted in too-fluid matrixes to be printable in a reproducible matter
296 at the selected temperature. Moreover, the reduction of the extrusion temperature to 70°C resulted
297 useless since the matrix flowed outside the edge of the (trans)dermal patch quickly after the
298 application of the backing layer. EuRL showed a similar behaviour only when 60% w/w TRI was
299 used. In the case of formulations designed with 40% w/w TBC the extrusion at 90°C led to a melt
300 that was too stiff to adhere to the backing layer, so the temperature was increased up 100°C. These
301 findings agreed with the complex viscosity (η^*) of the polymeric blend at 25°C (1.5 Hz), even if such
302 a temperature was significantly lower than extrusion one. The η^* -values of EuRS-based (trans)dermal
303 patches were lower than the equivalent EuRL formulations, justifying the worsening of the
304 printability of (trans)dermal patch. Indeed, at equal plasticizer concentration, the EuRS matrices were
305 more fluid than EuRL ones (**Table 1**). Moreover, TRI decreased more significantly the η^* -value than
306 TBC. These differences were more significant for EuRL-matrices (e.g., Form. **2** vs Form. **5**) than
307 EuRS ones (e.g., Form. **8** vs Form. **10**). These results agreed with rheological results obtained on
308 EuRL-based adhesive matrix prepared by solvent casting (Quaroni et al., 2018). Indeed, the
309 rheological properties of EuRL/TRI-based matrices showed a more liquid-like behaviour than
310 EuRL/TBC ones due to more significant interaction of TRI with polymeric chains.

311 The overall results suggested that η^* -values lower than 1 KPa/s were correlated to a high fluidity of
312 the extruded materials to be printed in a defined shape and size, whereas values higher than 15 KPa/s

313 to melt matrices too stiff to adhere to the backing layer and to obtain homogenous (trans)dermal
314 patches (Form. **1**, **Table 1**). For η^* -values ranged between 1 and 10 KPa/s, the formulations were
315 printable in a reproducible matter.

316 Starting from these results, the impact of the copolymer ratio was also tested using 50% w/w TBC or
317 40% w/w TRI (Forms. **12-17**, **Table 1**). In these cases, all the formulations showed η^* -values in the
318 range of printability of (trans)dermal patch, even if a slight decrease was observed increasing the
319 EuRS concentration within the matrix.

320 All the printed (trans)dermal patches **resulted homogeneous (Fig. 2)** with a reproducible thickness
321 ranging $50 \pm 10 \mu\text{m}$. Nevertheless, several formulations showed a too high cold flow (**Table 1**). In
322 particular, PSAs prepared with EuRL or EuRS with 60% w/w plasticizer failed the assay after one
323 month of storage. This phenomenon occurs when, at low frequencies (in the range 0.05-0.5 rad/s),
324 the G' values are relatively low, and G'' ones are predominant. In the case of printed (trans)dermal
325 patches, the cold flow was observed when η^* -value was lower than 3 kPa/s (at 1.5 Hz), and the ratio
326 between G' and $\tan \delta$ determined at 0.4 rad/s was lower than 0.2 kPa (Rohn, 1959).

327 Moving the attention to the adhesive properties, accordingly to Class and Chu, optimal tack properties
328 of the prepared placebo (trans)dermal patches may be reached with the G' -values between 5×10^4
329 and 2×10^5 Pa at frequencies between 0.005 and 0.05 rad/s (Rohn, 1959). In the case of printed
330 (trans)dermal patches, the higher σ_{max} and W -values were observed with G' -values around 10^3 - 10^4
331 Pa, supporting the acceptable adhesive properties of the matrices. Moreover, the Dahlquist's criterion
332 ($G' \leq 0.1$ MPa at 1 Hz) was fulfilled by most of the formulations, suggesting that adhesive matrices
333 were able to wet the adherend surface completely (Dahlquist, 1959). Indeed, exception made for
334 Form. **1** which showed a weak adhesion property, all the formulations showed G' -values lower than
335 10^5 Pa (**Fig. 1**). The G' -values of EuRS-based matrices ($\leq 10^3$ Pa) are significantly lower than those
336 of EuRL ones; however, the higher $\tan \delta$ values revealed a higher viscous behaviour of the former
337 matrices ($G'' > G'$) at low frequencies. In the case of EuRL matrices, when 40% w/w TRI was used

338 as a plasticizer, the tack parameters resulted significantly higher than those obtained from TBC-
339 containing matrices. However, this difference was significantly reduced, increasing the plasticizer
340 concentration up to 50% w/w, due to a prevalence of the viscous behaviour of the materials ($G'' >$
341 G').

342 EuRL matrices showed higher shear adhesion than EuRS matrices (e.g., Form. 1 vs Form. 7). This
343 feature is in agreement with the rheological data showing a higher storage modulus (G') in EuRL
344 matrices than in EuRS, at frequencies between 0.05 and 0.5 rad/s that is the range usually considered
345 to predict the shear adhesion (**Fig. 1**) (Rohn, 1959).

346 The results of 180° peel adhesion tests demonstrated that the forces required to peel away all the
347 printed (trans)dermal patches from the Teflon® surface were quite low. The type of plasticizer and
348 copolymer composition did not influence peel value. This result could be due to the low critical
349 surface tension of Teflon (Minghetti et al., 1999) which mimics the critical surface tension of the
350 clean human skin and requires a low force for the detachment. On the other hand, the use of a substrate
351 with a higher critical surface tension (i.e. steel) was tested but resulted not feasible since it caused an
352 adhesive failure for several formulations (data not shown).

353 However, it is noteworthy that the overall results of peel tests suggested that printed (trans)dermal
354 patches were more easy-to-peel than styrene-based matrices prepared with other hot-melt extrusion
355 techniques (Ma et al., 2013; Zhao et al., 2016).

356 In the case of EuRL/EuRS blends, the tack (σ_{\max} and W -values, **Table 1**) was influenced by the EuRS
357 concentration. In agreements with results obtained for EuRL and EuRS blends, the effects varied as
358 a function of the plasticizer type. In the presence of TBC, the higher the EuRS concentration, the
359 higher the σ_{\max} and W -values (Forms. 12-14, **Table 1**). On the contrary, the opposite trend was
360 observed for TRI-based formulations (Forms. 15-17, **Table 1**).

361 The shear adhesion studies showed a low cohesivity of the TBC-contained matrices, whereas
362 acceptable values were observed in the presence of TRI. Indeed, the shear adhesion of TRI-based
363 (trans)dermal patches (>140 min) was 7-fold higher than TBC-based ones (< 20 min). Although the
364 data of TRI series were lower than those obtained with other polymeric matrices prepared with hot-
365 melt extrusion techniques (Ma et al., 2013; Zhao et al., 2016), they agreed with those available in the
366 literature for marketed loco-regional patches (Cilurzo et al., 2015), whereas are significantly higher
367 than those obtained by nanofiber patches prepared by electrospinning (Shi et al., 2014). Moreover, a
368 direct correlation between the matrix resistance to flow and the EuRL/EuRS ratio was found. Indeed,
369 comparing matrices containing the same plasticizer, the higher the EuRL concentration, the higher
370 the shear adhesion value ($R^2 = 0.87$). This finding agreed with data published by Quaroni and co-
371 workers (Quaroni et al., 2018). The overall data confirms that the proposed preparation method does
372 not affect the adhesive performances of the (trans)dermal patches in comparison to the consolidated
373 solvent casting technique.

374

375 **3.3 Drug-loaded (trans)dermal patches**

376 Considering the pattern exhibited by placebo (trans)dermal patches, both KP and NT were loaded on
377 adhesive matrixes starting from the placebo formulations prepared using the 40% w/w TRI (**Table**
378 **2**).

379 The loading of KP and NT did not affect the printing of the (trans)dermal patches, and they were
380 reproducible enough to fulfil with the Ph Eur monograph on the uniformity of content (**Table 3**).
381 Moreover, the PSA appears homogeneous without a sign of crystallization grown (**Fig. 2**). Neither
382 for KP nor NT, no morphological differences were observed between the drug-loaded and placebo
383 PSA. *After the process, no significant degradation pattern of both KT and NT have been detected.*
384 *Although a deepened characterization of the physical state of both drugs was not performed, the*
385 *experimental data suggested no significantly variations were expectable based on previous evidence*

386 reported on the literature obtained with PSA-matrixes made of the same PSA (Cilurzo et al., 2008;
387 Quaroni et al., 2018).

388 When both drugs were loaded in the adhesive matrices, the fluidity of the extruded material was
389 increased, facilitating the printing of (trans)dermal patch. This evidence is also related to a reduction
390 of the shear adhesion values in comparison to placebo printed (trans)dermal patches (**Table 2**). For
391 examples, the shear adhesion value of Form. **16** (234 ± 45 min) decreased up to 3-fold and 9-fold
392 when KP (Form. **16-KP**: 64 ± 11 min) and NT (Form. **16-NT**: 25 ± 5 min) was loaded in the matrix,
393 respectively ($p < 0.05$, Student's T-Test). However, the observed reduction should have no impact on
394 the *in vitro* performances of the printed (trans)dermal patch onto patient skin since the observed
395 values remained comparable to other marketed cutaneous patches and medicated plasters (Minghetti
396 et al., 1999).

397 The *in vitro* release studies demonstrated that the release profiles from EuRL/EuRS matrices
398 depended on the type of loaded drug. Indeed, as shown in **Fig. 3**, the NT was released faster than KP
399 from the same adhesive matrices. For example, 80% of NT was released in less than 30 min from
400 Form. **4-NT**, whereas KP in 4 hours from the same adhesive matrix (Form. **4-KP**). This evidence was
401 in line with published papers that had demonstrated the chemical interactions between KP and acrylic
402 copolymer and their impact on the physicochemical features and the technological performance of
403 the drug-loaded dosage form (Eerikäinen et al., 2004; Musazzi et al., 2018a; Rassa et al., 2008).

404 Besides these results, it is noteworthy that the released rate constant of KP from Form. **4-KP** (**Table**
405 **3**) resulted slightly smaller but comparable to that obtained from a (trans)dermal patch with a similar
406 composition but prepared by solvent casting technique [$K = 0.78 \pm 0.01 \text{ h}^{-1}$ (Quaroni et al., 2018)].

407 These similarities in release profile suggested that, also for this property, the changes in preparation
408 methods did not alter the ability of the matrix in released the loaded drug. Moreover, the *in vitro* drug
409 release profiles also confirmed the role of copolymer ratio on the release of the drug through the
410 matrices. It is noteworthy that EuRL matrix was more permeable to water and drugs than EuRS
411 (Akhagari et al., 2006; Cilurzo et al., 2014a). The observed differences are also ascribable to a higher

412 swelling in aqueous solvents of EuRL compared to EuRS, especially around neutral pH (Akhagari et
413 al., 2006). As shown in **Table 3**, the higher the EuRL concentration in the matrix, the higher the
414 release rate constants. Indeed, regardless the loaded drug, the release rate constants increased in the
415 following order: EuRL/EuRS 0/1 (Forms. **9-KP**, **9-NT**) < EuRL/EuRS 1/1 (Forms. **16-KP**, **16-NT**)
416 < EuRL/EuRS 1/0 (Forms. **4-KP**, **4-NT**).

417 These results agreed with literature regarding the influence of EuRL/EuRS ratio on the *in vitro* and
418 *in vivo* performances of (trans)dermal patches (Aggarwal et al., 2013; Cilurzo et al., 2014a; Kusum
419 Devi et al., 2003; Mutalik and Udupa, 2004). Indeed, according to the well-known characteristics of
420 the two copolymers, the higher the concentration of EuRL in the matrix, the higher the permeability
421 of the matrix and, therefore, the higher the release rate of drugs. This effect is independent of the
422 physicochemical properties of the drug substance loaded in the matrix. Indeed, the addition of EuRS
423 to the formulation of (trans)dermal patch altered the diffusion/release mechanism of the drug. In
424 particular, 20% of EuRS can reduce the diffusion of verapamil significantly through a EuRL-based
425 adhesive matrix (Kusum Devi et al., 2003). Mutalik and Udupa confirmed this trend (Mutalik and
426 Udupa, 2004). From EuRL/EuRS-based transdermal patches, the drug release of glibenclamide, a
427 well-known hypoglycemic drug, was reduced when the EuRS concentration increased from 25% to
428 60% w/w.

429 It is noteworthy that the differences observed in the *in vitro* release profiles are not relevant in terms
430 of skin permeation of KP (**Fig. 4**). Indeed, even if the release rate constant of EuRL-based
431 (trans)dermal patches (Form. **4-KP**) resulted in more than two-time higher than EuRS-based
432 (trans)dermal patches (Form. **9-KP**), the permeation fluxes were superimposable (**Table 3**). Such
433 results are comparable to those obtained by other medicated plasters, regardless of the matrix
434 composition (Cilurzo et al., 2015; Quaroni et al., 2018) and agree with the general statement that the
435 permeation process is mainly related to the drug thermodynamic activity in the formulation (EMA,
436 2014). Indeed, the limiting step of drug permeation is the drug partition in the *stratum corneum* and
437 not the drug release from the matrix. Therefore, the observed differences in the release rate of both

438 drugs may have a negligible impact on the actual concentration gradient between the outer and inner
439 layers of the human epidermis, which is the real driving force of the permeation process. These
440 considerations also justify the permeation pattern of NT (**Fig. 4**). In this case, the EuRS-based matrix
441 permitted a high permeation (Form. **9-NT**; $Q_{24} = 387.12 \pm 29.10$) in comparison to EuRL-based
442 matrix (Form. **4-NT**; $Q_{24} = 215.48 \pm 38.56$) in contrast with the dissolution data (**Table 3**). In
443 agreement with the data discussed above, the decrease of the permeation flux of NT released by
444 EuRL-based matrix observed after seven hours was attributed to a variation of the drug
445 thermodynamic activity over time. The obtained results agreed with previously published data
446 obtained from a similar polymeric matrix (Cilurzo et al., 2008).

447

448 **4 Conclusions**

449 The printing of hot-melt PSA based on poly-ammonium methacrylates, such as EuRL, EuRS and
450 mixtures thereof, can be advantageously used for preparing or prototyping transdermal patches or
451 medicated plasters. The selection of polymer/plasticizer ratio and the composition of other excipients
452 can be easily optimized and controlled to guarantee suitable adhesive properties of the matrix and its
453 stability during the time. Interestingly, the biopharmaceutical performances of the (trans)dermal patch
454 (i.e., skin permeation) were not altered within the investigated formulative space, suggesting the high
455 robustness of the proposed technology. Also, the obtained results evidenced that the performances of
456 the printed (trans)dermal patches loaded with KP or NT are very close to that obtained by the
457 conventional casting technique. Thus, the hot-melt ram extrusion printing can be a feasible
458 technology in the production of very small batches for preliminary formulative studies, or
459 preclinical/exploratory trials during the pharmaceutical development of a medicinal product.
460 Moreover, it could be useful in the compounding of personalized cutaneous patches when the
461 treatment of skin diseases requires original patch shape.

462 In conclusion, printing technologies can be advantageously used to produce small batches of
463 (trans)dermal patches even if they require PSA appositely designed. As in the example reported in
464 the actual study, the use of a hot-melt printing technique requires a material which exhibits a suitable
465 viscosity to be printed at relatively lower temperatures than those generally required by a hot-melt
466 extrusion process (Thakkara et al. 2020), and acquires suitable viscoelastic performances at room
467 temperature to avoid cold flow and show acceptable adhesive properties. Starting from this proof-of-
468 concept, further studies are required to better investigate the impact of the printing on the chemical
469 and physical state of drug substances loaded in the (trans)dermal patches.

470

471 **Figures**

472

473 **Fig. 1** Evolution of G' (solid line), G'' (long-dashed line) and $\tan \delta$ (dotted line) as a function of
474 frequency. (A) EuRL patch formulations containing TRI and (C) TBC; (B) EuRS patch formulations
475 containing TRI and (D) TBC. Black line: formulations containing 40% w/w of plasticizer, grey line:
476 formulations containing 50% w/w of plasticizer and light grey line: formulations containing 40% w/w
477 of plasticizer. Tests were performed at 25°C.

478

479 **Fig. 2** Printed (trans)dermal patch during peeling off from the release liner (PSA: pressure-sensitive
480 adhesive matrix; BL: backing layer; RL: release liner) (A) and microscopic image of KP-loaded
481 patches (Form 4-KP), adhesive matrix plus backing layer, after removal of release liner (B). The
482 image was taken on printed patches stored at room temperature for six months. No signs of
483 crystallization were observable. The black spots detectable in the background belong to the intrinsic
484 opacity of backing layer.

485

486 **Fig. 3** In vitro release profiles of KP- (A) and NT-loaded patches (B) (Mean \pm St.Dev.; n =3). Solid
487 squares and lines: Forms **4-KP** and **4-NT**; Solid rhombus and dashed lines: Forms. **16-KP** and **16-**
488 **NT**; Solid circles and dotted lines: Forms. **9-KP** and **9-NT**.

489

490 **Fig. 4** In vitro permeation profiles of KP- (A) and NT-loaded patches (B) (Mean \pm St.Dev.; n =3).
491 Solid squares and lines: Forms **4-KP** and **4-NT**; Solid circles and dotted lines: Forms. **9-KP** and **9-**
492 **NT**.

493

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- 571

Table 1 Composition (%) of placebo patches used for screening the acceptable polymer/plasticizer ratio in terms of matrix printability, cold flow after one month of storage, rheological and adhesive properties. The matrix printability is expressed by the following score system: A (easily printable), B (printable not in a reproducible way), and C (not printable). For cold flow: N, the absence of cold flow; Y, the presence of cold flow.

Form	Composition (%)				Printability	Rheological properties			Adhesive properties			
	EuRL	EuRS	TBC	TRI		Cold flow ¹	η^* (kPa/s) ²	Cross over (rad/s)	Tack		Shear adhesion (min)	Peel adhesion (cN/cm)
									σ_{max} (kPa)	W (mJ)		
1	60	-	40	-	B	N	20.5	0.1	5.9±1.5	0.008±0.001	2062±1124	12.8±5.1
2	50	-	50	-	A	N	6.1	0.4	246.8±61.2	0.105±0.023	157±43	15.2±2.1
3	40	-	60	-	A	Y	1.6	2.2	₋₃	₋₃	₋₃	₋₃
4	60	-	-	40	A	N	11.5	0.2	218.0±17.0	0.053±0.013	396±79	12.5±0.5
5	50	-	-	50	B	N	4.0	2.5	252.5±49.7	0.065±0.038	170±20	3.5±2.4
6	40	-	-	60	C	Y	1.0	13.5	₋₃	₋₃	₋₃	₋₃
7	-	60	40	-	A	N	10.9	1.0; 17.6	292.2±43.3	0.193±0.060	553±385	50.3±19.5
8	-	50	50	-	B	Y	2.4	>100	₋₃	₋₃	₋₃	₋₃
9	-	60	-	40	B	N	7.6	3.4	125.2±85.3	0.093±0.059	181±10	14.2±2.9
10	-	50	-	50	B	Y	2.0	40.0	₋₃	₋₃	₋₃	₋₃
11	-	40	-	60	C	Y	0.5	> 100	₋₃	₋₃	₋₃	₋₃
12	37.5	12.5	50	-	A	N	4.2	25.0	167.1±35.7	0.068±0.025	17 ± 4	12.8±7.9
13	25	25	50	-	A	N	5.6	> 100	114.2±24.7	0.067±0.017	5±1	7.4±0.9
14	12.5	37.5	50	-	B	N	2.9	> 100	7.5±5.4	0.022±0.012	8±1	7.4±0.5
15	45	15	-	40	A	N	10.1	0.9	8.5±0.9	0.006±0.001	364±149	7.4±1.1
16	30	30	-	40	A	N	7.3	2.5	87.6±32.2	0.046±0.016	234±45	10.3±1.0
17	15	45	-	40	B	N	4.6	44.0	214.5±49.3	0.093±0.016	149±41	15.3±0.7

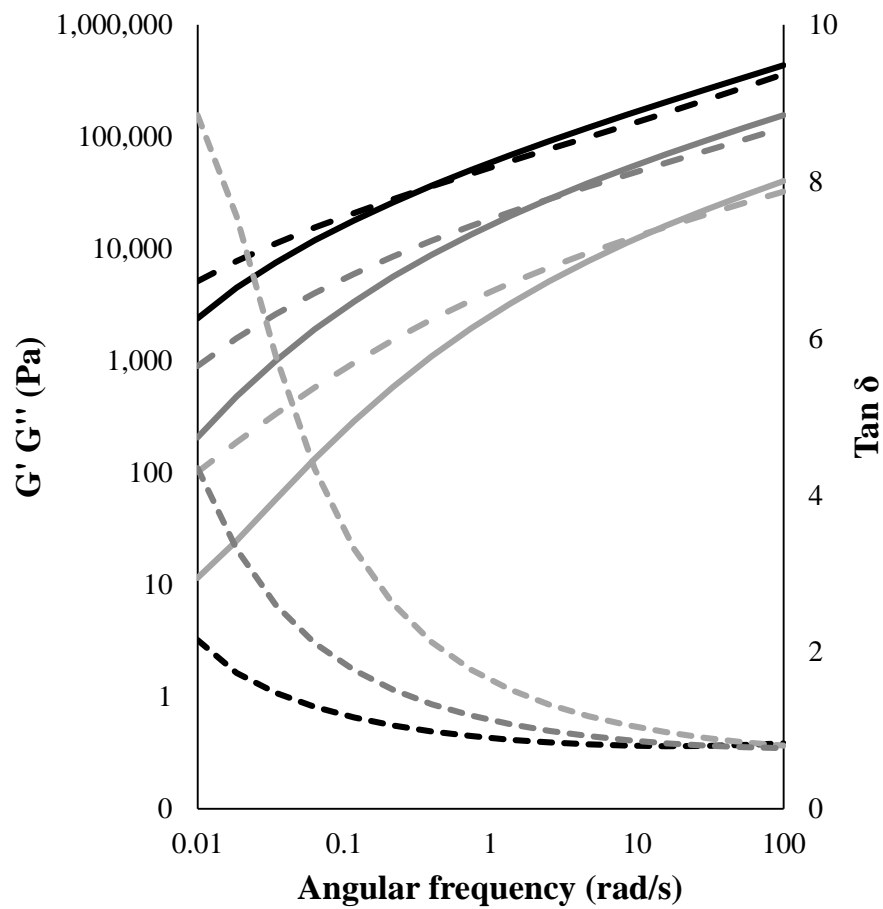
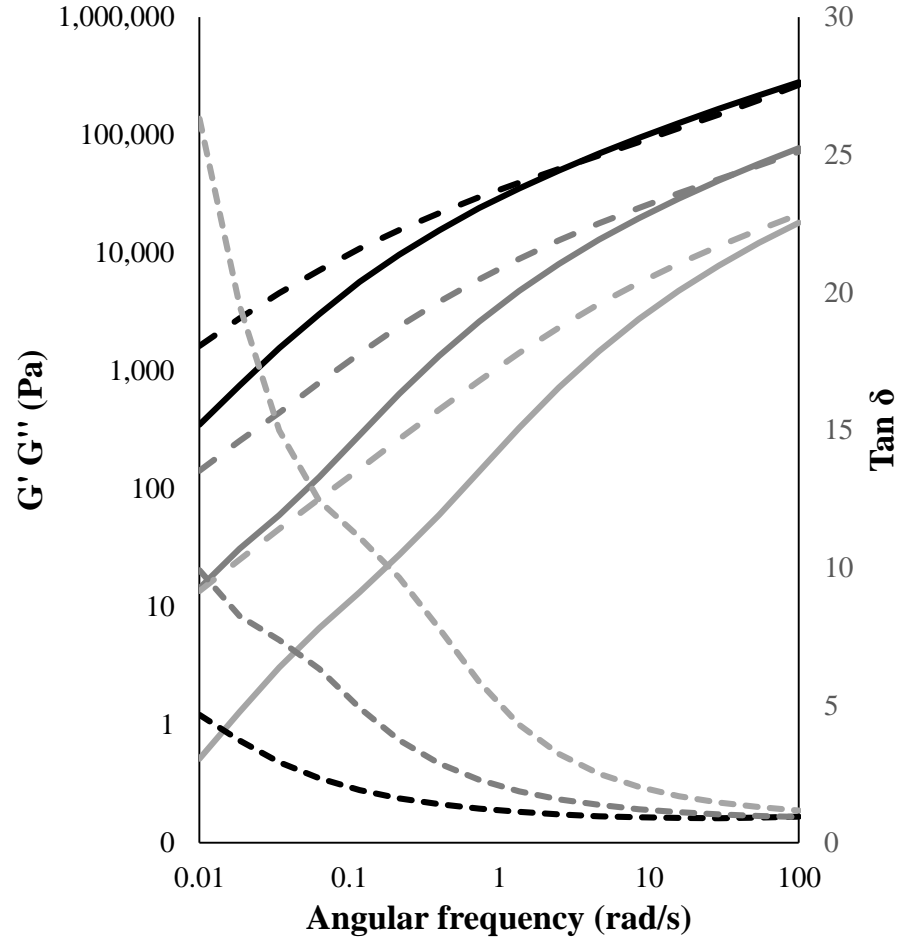
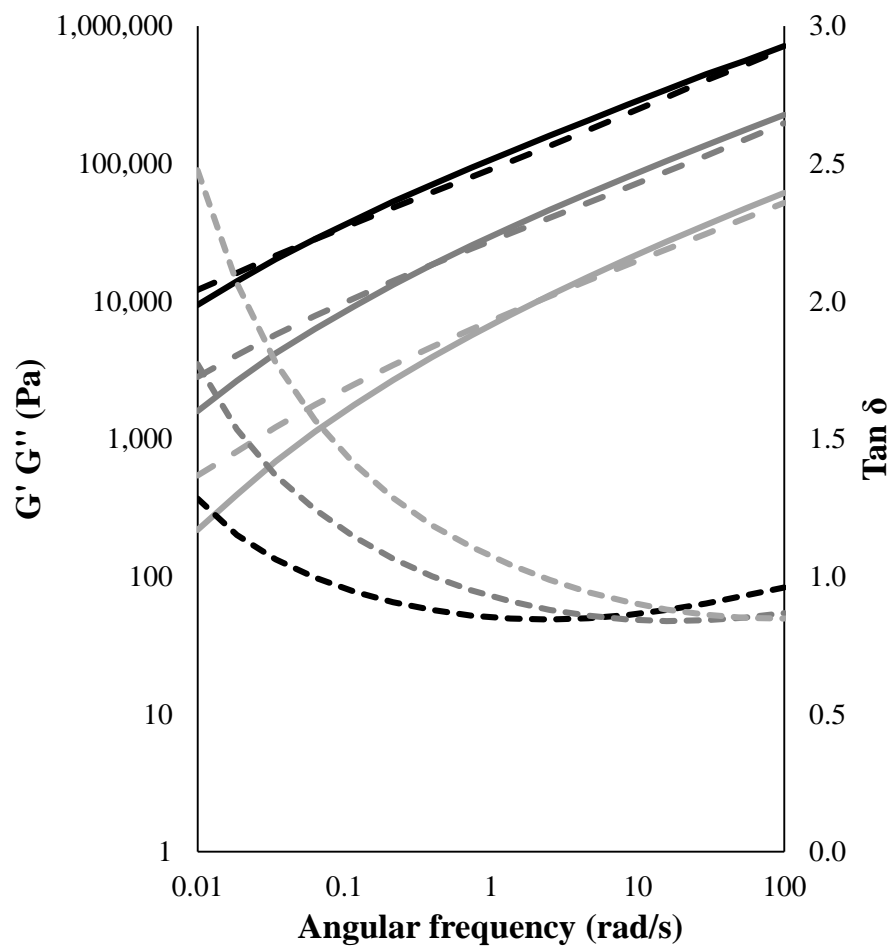
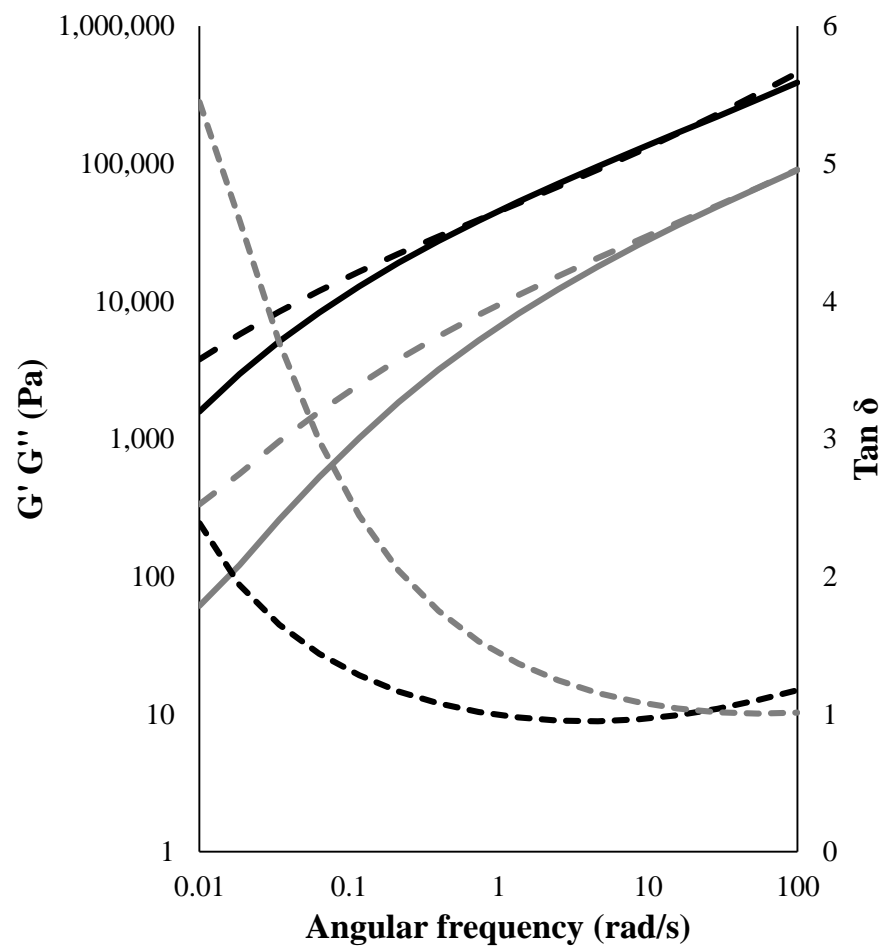
¹ 40°C, 1 month; ² determined at 1.5 Hz; ³ not determined since the cold flow was observed

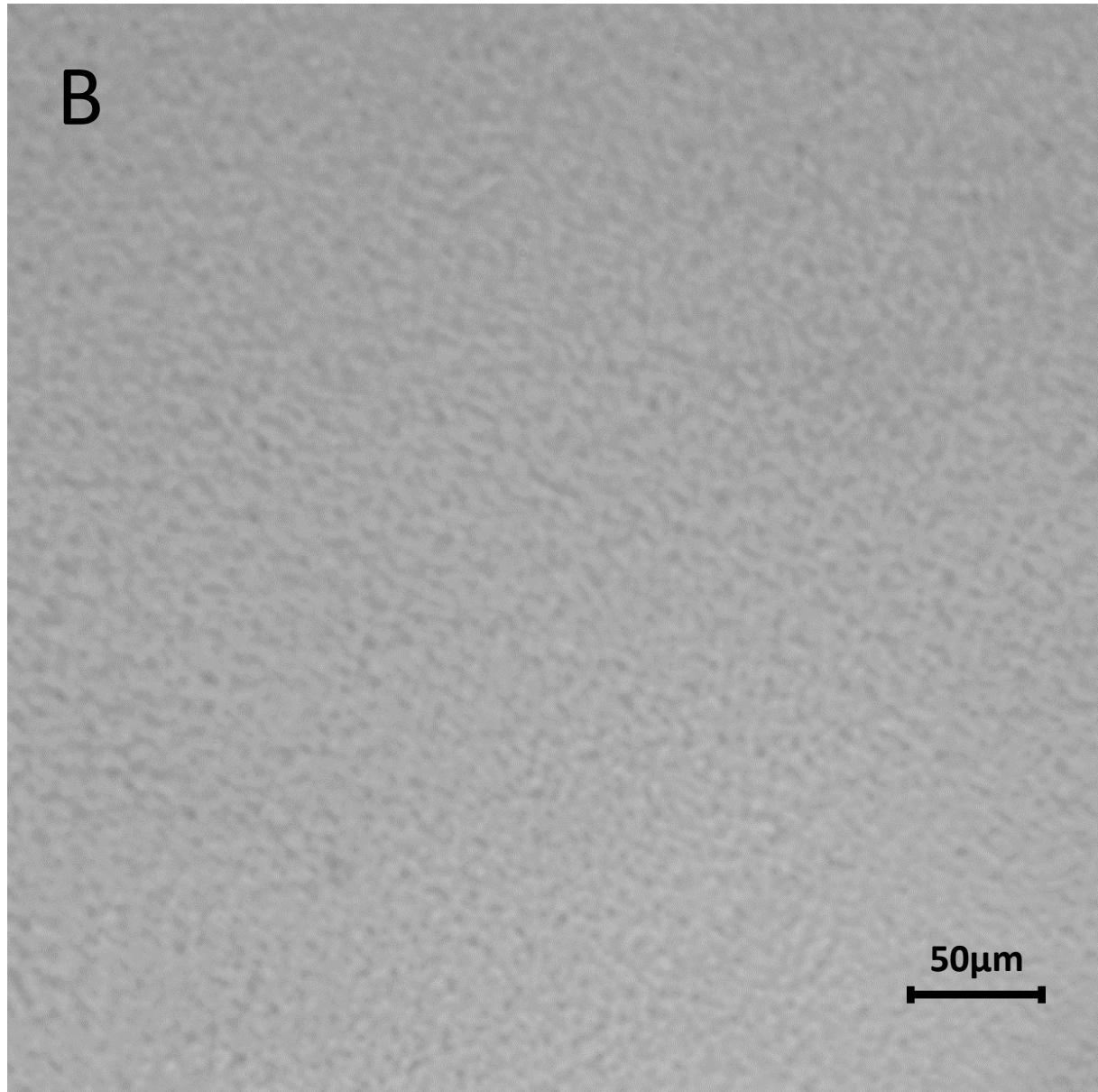
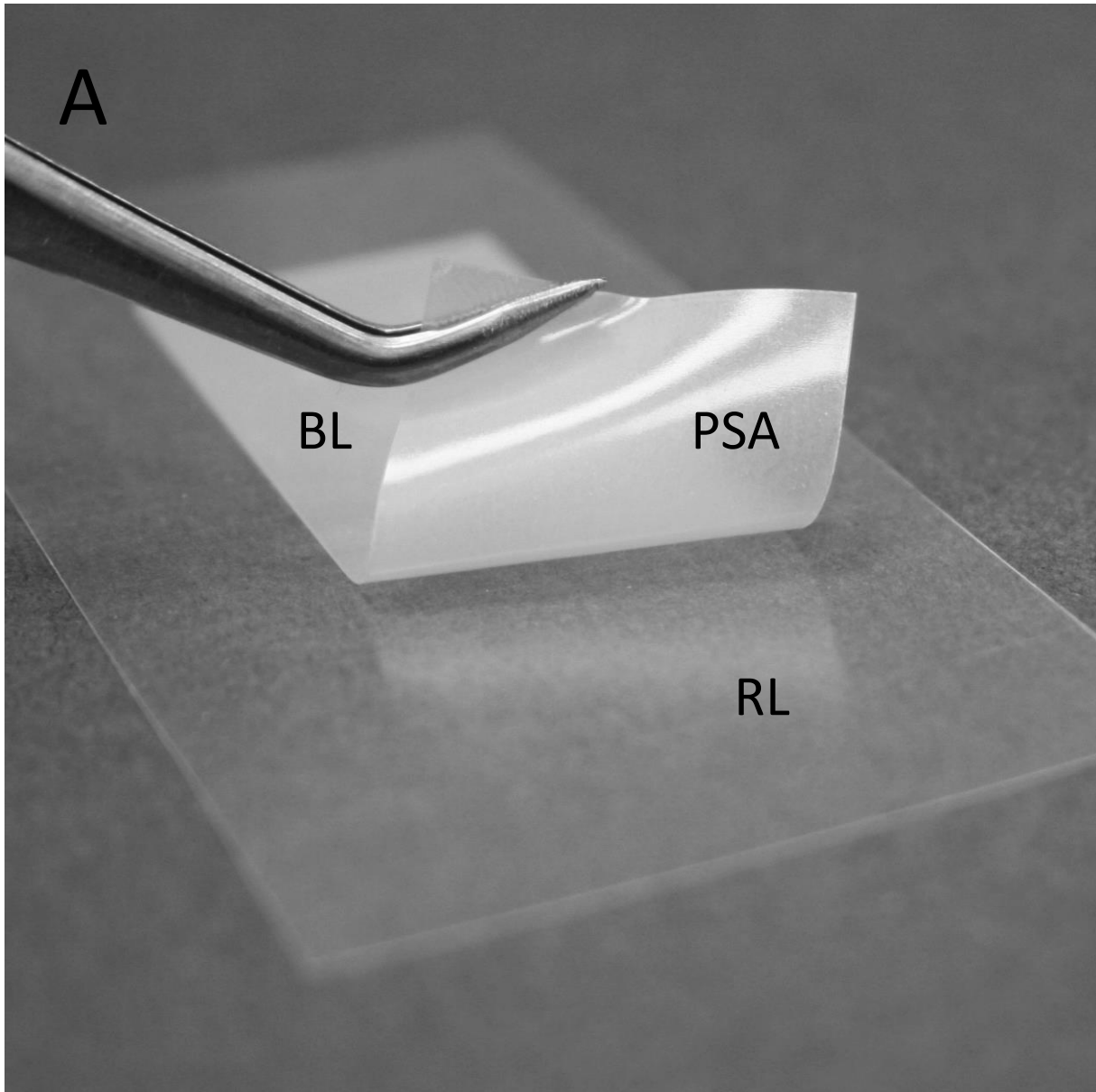
Table 2 Composition (%) of drug-loaded patches, thickness, and their characterization in term of cold flow after one month at 25°C or at 40°C, and adhesive properties (N: the absence of cold flow; Y: the presence of cold flow).

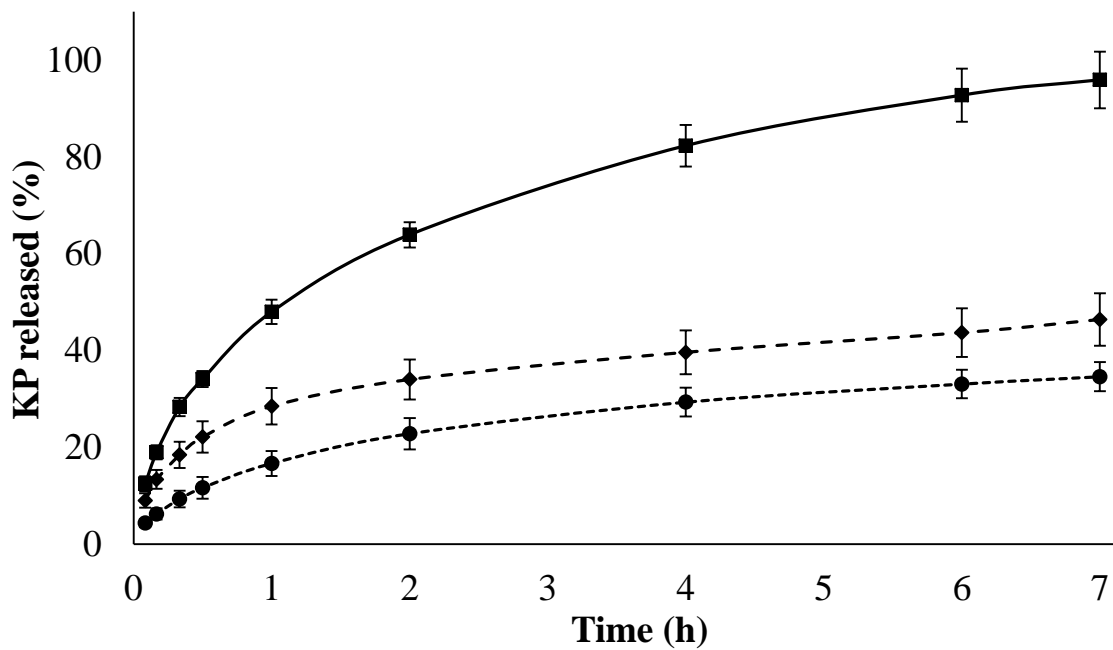
Form.	Composition (%)						Thickness (μm)	Cold flow		Adhesive properties	
	<i>EuRL</i>	<i>EuRS</i>	<i>TBC</i>	<i>TRI</i>	<i>KP</i>	<i>NT</i>		25°C	40°C	<i>Shear adhesion (min)</i>	<i>Peel adhesion (cN/cm)</i>
4-KP	58.60	-	-	39.06	2.34	-	54 ± 8	N	Y	66 ± 3	7.7 ± 0.4
9-KP	-	58.60	-	39.06	2.34	-	58 ± 14	N	Y	67 ± 3	14.9 ± 5.8
16-KP	29.30	29.30	-	39.06	2.34	-	59 ± 11	N	Y	64 ± 11	13.5 ± 1.3
4-NT	58.20	-	-	39.06	-	3.00	62 ± 13	N	N	81 ± 3	5.3 ± 0.4
9-NT	-	58.20	-	39.06	-	3.00	67 ± 9	N	N	21 ± 8	12.0 ± 0.7
16-NT	29.10	29.10	-	39.06	-	3.00	66 ± 16	N	N	25 ± 5	9.4 ± 0.8

Table 3 Drug content, release rate constant (K) and skin permeation flux (J) of printed drug-loaded patches (Mean \pm St.Dev.; n = 3; n.d.: not determined).

Form.	Drug	Drug content		K (h ^{-0.5})	J ($\mu\text{g}/\text{cm}^2/\text{h}$)
		$\mu\text{g}/\text{mg}$	$\mu\text{g}/\text{cm}^2$		
4-KP	KP	2.2 \pm 0.1	166.1 \pm 8.3	0.41 \pm 0.02	0.60 \pm 0.02
9-KP	KP	2.3 \pm 0.0	152.1 \pm 29.4	0.13 \pm 0.01	0.60 \pm 0.13
16-KP	KP	2.3 \pm 0.1	161.7 \pm 15.8	0.15 \pm 0.01	n.d.
4-NT	NT	2.3 \pm 0.1	158.6 \pm 35.1	2.61 \pm 0.05	15.28 \pm 3.07
9-NT	NT	3.0 \pm 0.5	196.6 \pm 12.2	0.29 \pm 0.07	20.38 \pm 3.13
16-NT	NT	2.2 \pm 0.4	136.5 \pm 13.7	1.36 \pm 0.09	n.d.

A**B****C****D**



A**B**