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Title: Retentive device for intravesical drug delivery based on water-induced shape memory response of poly(vinyl alcohol): design concept and 4D printing feasibility

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Keywords: shape memory polymer; poly(vinyl alcohol); hot melt extrusion; fused deposition modeling; 3D printing; 4D printing; intravesical delivery.

Corresponding Author: Dr. Lucia Zema, Ph.D.

Corresponding Author's Institution: Università degli Studi di Milano

First Author: Alice Melocchi

Order of Authors: Alice Melocchi; Nicoletta Inverardi; Marco Uboldi; Francesco Baldi; Alessandra Maroni; Stefano Pandini; Francesco Briatico-Vangosa; Lucia Zema, Ph.D.; Andrea Gazzaniga

Abstract: The use of shape memory polymers exhibiting water-induced shape recovery at body temperature and water solubility was proposed for the development of indwelling devices for intravesical drug delivery. These could be administered via catheter in a suitable temporary shape, retained in the bladder for a programmed period of time by recovery of the original shape and eliminated with urine following dissolution/erosion. Hot melt extrusion and fused deposition modeling 3D printing were employed as the manufacturing techniques, the latter resulting in 4D printing because of the shape modifications undergone by the printed item over time. Pharmaceutical-grade poly(vinyl alcohol) was selected based on its hot-processability, availability in different molecular weights and on preliminary data showing water-induced shape memory behavior. Specimens having various original and temporary geometries as well as compositions, successfully obtained, were characterized by differential scanning calorimetry and dynamic-mechanical thermal analysis as well as for fluid uptake, mass loss, shape recovery and release behavior. The samples exhibited the desired ability to recover the original shape, consistent in kinetics with the relevant thermo-mechanical properties, and concomitant prolonged release of a tracer. Although preliminary in scope, this study indicated the viability of the proposed approach to the design of retentive intravesical delivery systems.



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*J. Siepmann, University of Lille, France
Editor-in-Chief of International Journal
of Pharmaceutics*

Milan, November 16th 2018

Subject: manuscript submission

Dear Editor,

we are pleased to submit for publication in International Journal of Pharmaceutics our manuscript entitled “Retentive device for intravesical drug delivery based on water-induced shape memory response of poly(vinyl alcohol): design concept and 4D printing feasibility”, by A. Melocchi, N. Inverardi, M. Uboldi, F. Baldi, A. Maroni, S. Pandini, F. Briatico-Vangosa, L. Zema, A. Gazzaniga.

The work reported is an investigation into the water-induced shape memory response of pharmaceutical-grade poly(vinyl alcohol), having water solubility and hot-processability characteristics, for the development of an indwelling drug delivery system intended for intravesical administration involving no invasive removal procedures. Such delivery systems would highly be advantageous in the management of bladder diseases because, by compensating for the urinary drug washout, they could enhance the therapy efficacy and overcome discomfort and bacterial infections connected with repeated catheterization, also bringing social and economic benefits. The design of the delivery system encompasses *i*) temporary shape suitable for administration *via* catheter, *ii*) original shape to be spontaneously recovered on contact with biological fluids, suitable for organ retention, and *iii*) dissolution/erosion for final elimination. Samples having different shapes and composition were manufactured by hot melt extrusion and fused deposition modeling 3D printing, enabling personalization of the treatment. Interestingly, the use of a 3D printing technique in combination with that of shape memory polymers (SMPs) provides the basis for 4D printing in view of the programmed changes in shape of the printed system over time. The use of SMPs hereby proposed could represent a deeply innovative strategy for effective bladder retention.



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We the undersigned declare that:

- this manuscript is original, has not been published before and is not currently being considered for publication elsewhere;
- there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome;
- the manuscript has been read and approved by all named authors and there are no other persons who satisfied the criteria for authorship but are not listed.

Sincerely Yours,

Francesco Briatico-Vangosa

Lucia Zema

**Retentive device for intravesical drug delivery based on water-induced shape memory
response of poly(vinyl alcohol): design concept and 4D printing feasibility**

Dear Prof. J. Siepmann, Ph.D.

Editor-in-Chief of International Journal of Pharmaceutics

We would like to thank the Reviewers for providing helpful comments and appreciating our work. Please find below a point-by-point outline of how the manuscript has been modified accordingly.

Reviewer #2:

General comments

The graphical abstract should be more immediate and give a sharp message.

We thank the Referee for the suggestion. The graphical abstract was accordingly modified to be simpler and provide a sharp message.

The scope of the paper is confined to a few lines in the introduction. Please expand and anticipate the various steps envisaged and describe/justify the techniques /methods proposed to fulfill the scope. This would help understanding on behalf of a less skilled reader.

The scope of the manuscript was expanded to include the various experimental steps/methods envisaged and, as requested by Reviewer #3, to justify the choice of poly(vinyl alcohol).

The concept of shape memory polymers is not immediate and deserves to be better explained. Even the concept of 4D printing should be worked out and made more explicit.

We agree with the Referee that the concepts of shape memory polymers and 4D printing would deserve more in-depth explanation. We have made effort in this respect, also adding related references.

Overall the idea is very innovative and the paper deserves publication.

Reviewer #3:

The manuscript submitted by Melocchi et al. combines the use of a new technology with the exploration of materials properties in a potential application with high clinical impact. Overall the manuscript is well designed and experiments carefully performed, generating data discussed in detail.

However, some points should be considered as follows:

- Abstract - the abstract does not entirely reflect the work with too many general considerations and less information about the work itself. An improved abstract should be considered.

We have revised the abstract following the Referee's suggestions, deleting too general considerations and adding information about the experimental work performed.

- Keywords - are more likely key expressions and some key words are not relevant for the scope of the manuscript.

We have updated the keywords avoiding key expressions that were less related to the work performed.

- A list of abbreviations would help to better understand and follow the text.

A list of the abbreviations used in the manuscript has been provided.

- Introduction - very little justification is provided to support the choice of PVA as a key material for the manufacture of the matrices.

The introduction section has been revised providing justification for the choice of poly(vinyl alcohol) and it was also expanded to include the various experimental steps/methods envisaged in the research work, as requested by Reviewer #2.

- Materials and methods - there is no justification for the grades and only 2 grades of PVA were considered. Furthermore why glycerol was considered. The reviewer believes that preliminary work pointed out to the use of these materials, but if that was the case, authors should refer the fact to provide a proper background for their selection. Likewise, authors do not provide any justification to support the processing conditions (Table 1) for both HME and FDM, particularly the selection of temperature and torque. Furthermore why extrudates had to be pulled and forced to pass through a caliper (lines 149-150)?

The Referee is right about the use of only 2 grades of poly(vinyl alcohol). Actually, we preliminarily investigated more, though processing turned out very critical for poly(vinyl alcohol) with higher molecular weights, thus requiring further investigation and process design studies. For this reason, we decided to go ahead with the grades here presented, which offered a good compromise between processability and softness of the polymer once hydrated, which is related to the expected performance of the system over time. However, we are already expanding our investigation including further grades of poly(vinyl alcohol), for which greater processing issues are being faced.

Glycerol was selected based on the review of the scientific literature, testifying its wide use as plasticizer for poly(vinyl alcohol), and on experience we previously gained on hot melt

extrusion and fused deposition modeling of such a polymer. This was better clarified in the text, also including relevant literature references.

Considering HME and FDM processes, suitable operating conditions were selected through a preliminary set-up relying on the expertise acquired and on a trial-and-error approach depending on the evaluation of the product quality in terms of aspect, homogeneity, adherence to previously set specifications (e.g. dimensions) and reproducibility. With regard to pulling and forcing extrudates to pass through a caliper, this was required in order to calibrate the filament diameter to counteract possible swelling phenomena of the extrudate. This in-process control would help in reducing the amount of final product out of the diameter specifications previously set, because filaments having diameter greater than 1.80 mm would be unsuitable for 3D printing by the equipment in use (a final control of diameter is also carried out after cooling). In industrial manufacturing plants, this issue is solved by the presence of a laser unit downline of the extruder to control the filament diameter before spooling. When portions out of specifications are revealed, a signal is automatically transmitted to the equipment to adjust the process conditions (e.g. screw and spooling speed), thus correcting the filament size.

We agree with the referee that the above details were missing in the manuscript and that literature references would not be enough for the reader. Therefore, we have tried to improve the text accordingly.

– Results and Discussion

Section 3.2 does not refer the reproducibility of the systems. Can it be assumed that only 1 sample was prepared and compared?

We agree with the Referee that Section 3.2 does not provide information on the reproducibility of the system. The work performed is indeed very preliminary focusing on a novel subject and reports data relevant to single samples for each formulation and shape under study. This should now be clearer in the Methods Section after the changes introduced. Actually, based on our knowledge, the use of a single curve to represent a time/temperature dependent response is not uncommon in scientific papers on shape memory polymers belonging to fields other than pharmaceuticals and is also related to the challenges involved in the manual programming of the temporary shape of the specimen in a lab setup.

This section also fails to produce more evidence on the relationship between the materials properties', the processing conditions and the resultant printed materials.

We agree with the Referee that evidence on the relationship between the material properties, processing conditions and performance of the resulting systems have not been exhaustively faced in Section 3.2. We are aware that these aspects are of utmost importance, particularly for

optimization and scale-up of the production processes, and we will definitely be committed to deepen our research to include the above-mentioned topics in the future. Although an effort was made to introduce changes into this Section, we would like to point out that the fine-tuning of its manufacturing processes was not the focus of the current work and its goal was rather to demonstrate the possibility of exploiting the water-induced shape memory behavior of a polymer of pharmaceutical grade for the development of a new drug delivery system. We hope that our preliminary results may be considered as an interesting starting point

Surprisingly, due to the authors' expertise in the area, section 3.3 is over summarized and little related with the previous section. Indeed the water contributes to the memory activation together with the temperature. Furthermore figure 7 cannot be read by itself and description of FU and RDM could not be found in the text. As it is, the value of this section is hard to recognise in the manuscripts context. An improved connection between the sections is deemed required for an improved understanding of the work.

Section 3.3 was reworded in an effort to strengthen its connection with the previous one and highlight the relevance of fluid uptake and residual dry mass experiments for the overall performance of the system. Further comments to the results obtained have also been reported.

Following Referee's suggestion, we have tried to make Figure 7 more readable. Moreover, as requested by the Referee, a list of abbreviations and relevant explanation, including FU and RDM, has been included at the beginning of the manuscript.

- Conclusions - overall conclusions are correct although further evidence on the relationship between the materials, processing conditions and products properties would have been of great benefit for the reader.

As stated above in response to the comments of Reviewer #3 to section 3.2, because the goal of our work was necessarily limited to investigating the viability of hot-processing of pharmaceutical-grade poly(vinyl alcohol) having water-induced shape memory response in the development of a retentive intravesical delivery systems, we do not unfortunately feel like broadening the Conclusions, which have to be strictly related to the aim and reflect the work performed.

Comments from the editor:

- 1) Could you please indicate a little bit more clearly what you mean by "4D printing" in the abstract?

We have made an effort to clarify what is meant for 4D printing, both in the abstract, in a more synthetic form due to the limited word count, and more into detail in the Introduction section, also following the request of Reviewer #2.

- 2) Could you please add scale bars to Figures 3 and 8?

We have added scale bars to Figures 3 and 8.

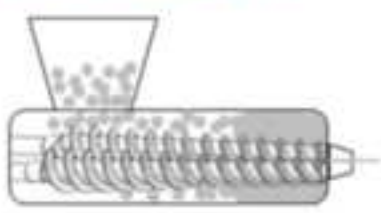
- 3) Figures 4 - 6: Could you please increase the size of the text and numbers (so that they are clearly visible, even in a print version)?

We have increased the size of the text and numbers in Figures 4 and 6 to make them clearly visible.

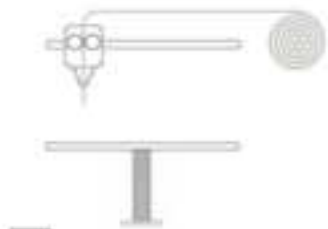
- 4) Tables 4 and 7: Could you please indicate what the lengths of the grids in the pictures are?

We have indicated the length of the grids in the pictures reported in Tables 4 and 7.

Hot Melt Extrusion



Fused Deposition Modeling



shape enabling
catheter administration

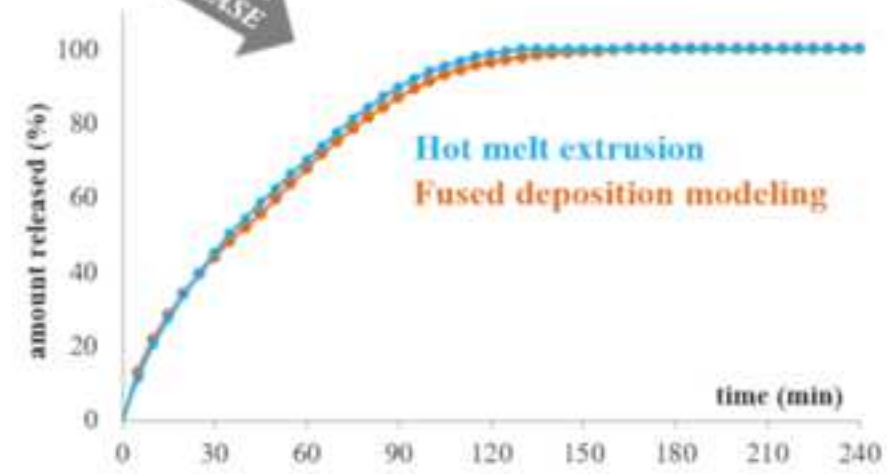
PROGRAMMING



shape enabling
bladder retention



time



1 **Retentive device for intravesical drug delivery based on water-induced shape**
2 **memory response of poly(vinyl alcohol): design concept and 4D printing**
3 **feasibility**

4
5 A. Melocchi^{a1}, N. Inverardi^{b1}, M. Uboldi^a, F. Baldi^b, A. Maroni^a, S. Pandini^b, F. Briatico-Vangosa^{c*},
6 L. Zema^{a*}, A. Gazzaniga^a

7
8 ^aDipartimento di Scienze Farmaceutiche, Sezione di Tecnologia e Legislazione Farmaceutiche
9 "Maria Edvige Sangalli", Università degli Studi di Milano, Milano, Italy;

10 ^bDipartimento di Ingegneria Meccanica e Industriale, Università degli Studi di Brescia, Brescia,
11 Italy;

12 ^cDipartimento di Chimica, Materiali e Ingegneria Chimica "G. Natta", Politecnico di Milano,
13 Milano, Italy.

14 ¹These authors contributed equally to the work.

15 *Corresponding authors: Lucia Zema, telephone: +39 02 50324654, e-mail: lucia.zema@unimi.it, and
16 Francesco Briatico-Vangosa, telephone: +39 02 23993290, e-mail: francesco.briatico@polimi.it

17 **Abstract**

18 The use of shape memory polymers exhibiting water-induced shape recovery at body temperature
19 and water solubility was proposed for the development of indwelling devices for intravesical drug
20 delivery. These could be administered *via* catheter in a suitable temporary shape, retained in the
21 bladder for a programmed period of time by recovery of the original shape and eliminated with urine
22 following dissolution/erosion. Hot melt extrusion and fused deposition modeling 3D printing were
23 employed as the manufacturing techniques, the latter resulting in 4D printing because of the shape
24 modifications undergone by the printed item over time. Pharmaceutical-grade poly(vinyl alcohol)
25 was selected based on its hot-processability, availability in different molecular weights and on
26 preliminary data showing water-induced shape memory behavior. Specimens having various original
27 and temporary geometries as well as compositions, successfully obtained, were characterized by
28 differential scanning calorimetry and dynamic-mechanical thermal analysis as well as for fluid
29 uptake, mass loss, shape recovery and release behavior. The samples exhibited the desired ability to
30 recover the original shape, consistent in kinetics with the relevant thermo-mechanical properties, and
31 concomitant prolonged release of a tracer. Although preliminary in scope, this study indicated the
32 viability of the proposed approach to the design of retentive intravesical delivery systems.

33

34 **Keywords:** shape memory polymer; poly(vinyl alcohol); hot melt extrusion; fused deposition
35 modeling; 3D printing; 4D printing; intravesical delivery.

36 **List of abbreviation**

37 3D: three dimensional

38 4D: four dimensional

39 α : angle between the two arms of U- and I-shaped samples during recovery

40 α_p : angle obtained in the programming phase of shape recovery experiments

41 CAD: computer-aided design

42 CFF: caffeine

43 DSC: differential scanning calorimetry

44 DMTA: dynamic-mechanical thermal analysis

45 E' : storage modulus

46 E'_{Room} : storage modulus at room temperature

47 E'_{Tdef} : storage modulus at deformation temperature

48 FDM: fused deposition modeling

49 FU: fluid uptake

50 GLY: glycerol

51 HME: hot melt extrusion

52 N_{final} : number of windings of helical-shaped samples at the end of recovery

53 N_0 : number of windings of helical-shaped samples before programming

54 PVA: poly(vinyl alcohol)

55 RDM: residual dry mass

56 RI: recovery index

57 RI_{final} : final recovery index

58 SMP: shape memory polymer

59 T_{def} : deformation temperature

60 T_g : glass transition temperature

61 T_{room} : room temperature

- 62 $t_{10\%}$: time needed to reach 10% of drug release
- 63 $t_{90\%}$: time needed to reach 90% of drug release
- 64 $t_{RI\text{final}}$: time needed to reach final recovery index
- 65 W_m : mass of the wet sample on withdrawal
- 66 W_d : mass of the sample after drying
- 67 W_i : initial mass of the sample

68 **1. Introduction**

69 The bladder is a muscle-epithelial sac responsible for the collection of waste substances from the
70 systemic circulation, coming from the kidneys, and their elimination as urinary fluids (GuhaSarkar,
71 and Banerjee, 2010, Hsu et al, 2013, Zacchè et al., 2015). Considering its pivotal role in the
72 homeostasis of the human body, any change in its functionality, even caused by the natural aging
73 process or brought about by the onset of diseases, is necessarily associated with inconveniences of
74 different extent. Vesical diseases, such as atonic and hyperactive bladder, interstitial cystitis and
75 cancer, are widespread in individuals of different age and gender. However, their incidence increases
76 in elderly people, who represent the population segment of developed countries in continuous growth
77 and whose therapeutic treatments have great impact on healthcare expenses. The pharmacological
78 therapy of such pathologies involves both systemic administration, mainly by the oral route, and *in*
79 *situ* transurethral instillation of different active ingredients. Topical administration of drugs offers
80 several advantages, *e.g.* to reduce the systemic side effects and avoid possible presystemic elimination
81 mainly by the liver (first-pass effect), thus also allowing lower drug strengths to be used. Currently,
82 solutions, suspensions or emulsions containing one or more drugs are instilled into the bladder
83 through a catheter, inserted directly into the urethra of the patient and then clamped off for a pre-
84 determined time period (from few minutes up to at least 1 h for chemotherapy), before being drained
85 or normally excreted after withdrawal of the catheter. In the case the latter is removed immediately
86 after instillation and the patient is asked to keep the solution in the bladder for the longest possible
87 time, the maximum residence time of drugs within the bladder hardly exceeds 2 h, even when fluid
88 intake is avoided. With the aim of counteracting the drug washout, repeated instillations are thus
89 required, and this may entail other complications, such as primarily the onset of infections.

90 In order to maintain effective concentrations of the bioactive molecules within the bladder, various
91 strategies have been pursued such as the use of bioadhesive liposome- or thermosensitive hydrogel-
92 based formulations (Cima et al., 2014, Farokhzad et al., 2006, Nirmal et al. 2010, Tyagi et al., 2016).
93 One of the most innovative approaches to intravesical delivery is represented by indwelling systems

94 administered transurethrally *via* catheter, that are designed to remain in the bladder for longer time
95 periods (*e.g.* weeks). This resembles the concept of expandable gastroretentive dosage forms, the
96 original size of which is reduced, *e.g.* by folding, into a carrier system such as a capsule: after
97 administration, the carrier dissolves or opens up in stomach and the unit conveyed recovers a
98 significantly larger spatial encumbrance due to swelling or unfolding processes that prolong its gastric
99 retention time (Klausner et al., 2003). Analogously, bladder retention was obtained through either an
100 increase in the size of the devices (*e.g.* UROS, Situs Corporation) or a change in the relevant geometry
101 after being positioned into the organ (*e.g.* LiRIS, TARIS Biomedical). The success of the indwelling
102 drug delivery systems described so far is still limited due to their poor tolerability, mainly associated
103 with relatively large dimensions, density higher than that of urine and need for a removal procedure
104 at the end of the treatment (Lee and Choy, 2016, Lee and Cima, 2011, Nickel et al., 2012). The idea
105 of a biodegradable indwelling system that would not involve subsequent removal was preliminarily
106 proposed (Tobias et al., 2010). However, the mechanism of retention (*e.g.* based on size increase or
107 on geometry variation) was not clearly defined.

108 Over the last few years, **shape memory polymers (SMPs)** have drawn great interest in the area of
109 advanced systems intended for biomedical applications (Behl and Lendlein, 2007, Chan et al., 2016,
110 El Feninat et al., 2002, Lendlein and Langer, 2002, Lendlein et al., 2010, Sokolowski et al., 2007,
111 Yahia, 2015). **They belong to smart materials capable of *i*) memorizing a permanent/original shape,**
112 ***ii*) being fixed, under appropriate temperature conditions and mechanical stress, to a temporary shape**
113 **and *iii*) being triggered, by an external *stimulus* such as a change in temperature, light, moisture,**
114 **magnetic field or electrical current, to spontaneously recover the memorized stress-free permanent**
115 **shape (Liu et al., 2007; Hager et al., 2015; Huang et al., 2010). Microstructural changes of the polymer**
116 **are responsible for shape fixing and shape recovery, the latter relaxation step being associated with**
117 **elastic deformation stored during previous manipulation.**

118 **In this respect, much attention has been focused on SMP-based devices in which shape changes could**
119 **be obtained at body temperature.** Once introduced into the human body, these would be able to modify

120 their shape thanks to exposure to 37 °C, thus performing their function. Interestingly, in a particular
121 class of SMPs, shape modifications can be triggered not only by heating but also through contact with
122 water (*i.e.* water-induced shape memory effect). Such SMPs are hydrophilic polymers for which
123 water taken up acts as a plasticizer and reduces the temperature required to activate the shape memory
124 response (Yang et al., 2004). In addition, SMPs characterized by water-induced shape memory
125 behavior and suitable thermoplastic properties could be subjected to hot-processing *via* forming
126 manufacturing techniques, such as **hot melt extrusion (HME)**, injection molding and **fused deposition**
127 **modeling (FDM)** 3D printing, which are well-known to yield high versatile geometries, details and
128 sizes of products. **Notably, the combined use of 3D printing technologies and SMPs has recently led**
129 **to the new concept of 4D printing, intended as fabrication *via* 3D printing of items capable of self-**
130 **transforming after production in terms of morphology, and thus possibly of functionality, in response**
131 **to an external *stimulus* (Ding et al., 2017, Gao et al., 2016, Lee et al., 2017; Maniruzzamann 2018).**
132 **As compared with 3D printing, 4D printing involves the use of smart materials and also an advanced**
133 **design, which has to take account of the original shape, the temporary shape, the transformations**
134 **undergone by the object to shift from one another and relevant mechanisms. The time frame in which**
135 **the original shape is recovered represents the 4th dimension. In spite of the huge potential held, major**
136 **applications of 4D printing in the development of drug delivery systems are yet to come.**
137 **Based on such premises, the aim of the present work was to study the possible water-induced shape**
138 **memory response of specimens fabricated from poly(vinyl alcohol) (PVA) of pharmaceutical grade**
139 **by means of hot-processing techniques, namely HME and FDM. In particular, PVA was chosen in**
140 **view of its known suitability for hot-processing and on preliminary results pointing out its water-**
141 **induced shape memory behavior. Indeed, such a property could advantageously be exploited for the**
142 **development of intravesical retentive systems, *i.e.* devices suitable for administration *via* catheter in**
143 **the programmed/temporary shape and for bladder retention following spontaneous recovery of the**
144 **permanent/original shape. Thanks to its slow interaction with aqueous fluids and related dissolution,**
145 **it was deemed to hold potential as the main component of an indwelling drug delivery system for**

146 prolonged release, with no need for being removed thanks to its erosion/dissolution over time.
147 Moreover, the release rate could interestingly be tuned by selecting the polymer molecular weight.
148 The feasibility of 4D printing in the manufacturing of such a device was preliminarily evaluated by
149 characterizing the specimens obtained for thermo-mechanical properties, water-induced shape
150 recovery, fluid uptake, mass loss as well as release behavior, using samples containing an analytical
151 tracer.

152

153 **2. Materials and Methods**

154 **2.1 Materials**

155 **PVA** of different grades (Gohsenol™ EG 05P and Gohsenol™ EG 18P, Nippon Gohsei, J) (PVA05
156 and PVA18); glycerol, GLY (Pharmagel, I); caffeine, CFF (A.c.e.f, I, melting point 238 °C).

157

158 **2.2. Methods**

159 2.2.1 Preparation of PVA-based formulations

160 Plasticized PVA formulations containing 15% by weight of GLY calculated on the dry polymer,
161 indicated as PVA05GLY and PVA18GLY, were prepared by kneading. PVA powder, previously
162 dried in an oven (40 °C for 24 h), was placed in a mortar and the liquid plasticizer was added dropwise
163 under continuous mixing. The resulting mixture was oven dried at 40 °C for 8 h. Afterwards,
164 aggregates were ground by means of a blade mill and the < 250 µm powder fraction was recovered.
165 A tracer-containing formulation, indicated as PVA05GLY-CFF, was prepared immediately before
166 processing by mixing in a mortar CFF powder, previously desiccated at 40 °C in an oven for 24 h,
167 with PVA05GLY in a 1:9 weight ratio.

168

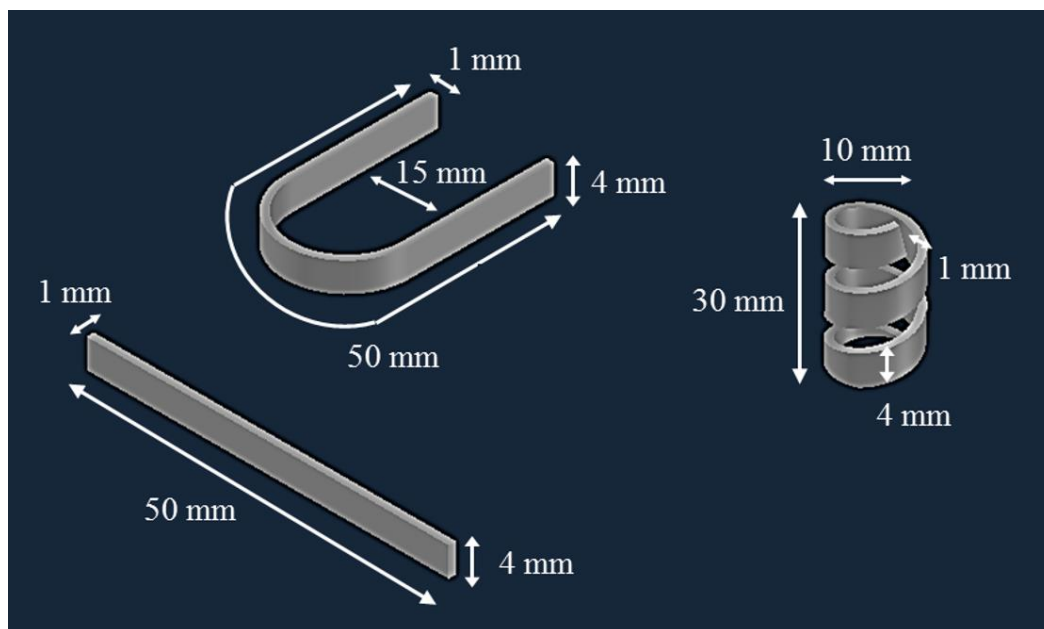
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170

171 2.2.2 Manufacturing of PVA-based samples

172 Specimens having different geometries were prepared by HME and FDM. Virtual models of the
173 straight bar (I-shape), U-shaped and helix items designed are reported in Figure 1.

174



175

176 **Figure 1:** virtual models with dimensional details of items having original I-, U- and helix-shapes.

177

178 2.2.2.1 Extrusion

179 HME was performed by a twin-screw extruder (Haake™ MiniLab II, Thermo Scientific, US-WI)
180 equipped with counter-rotating screws. The material was extruded through a rectangular cross-section
181 die (4 x 1 mm). In Table 1, the polymeric formulations and processing conditions are reported. Both
182 were selected through a preliminary setup based on evaluation of the product quality (e.g. aspect,
183 homogeneity, compliance with previously set size specifications and reproducibility), taking
184 advantage of the experience previously acquired on hot-processing of PVA (Melocchi et al., 2015b,
185 2016). Particularly, GLY was chosen as the plasticizer based on its widely reported use with PVA
186 (Jang and Lee, 2003; Lin and Ku, 2008; Mohsin et al., 2011).

187 I-shaped samples of 50 mm in length were obtained by cutting. U- and helix-shape items required
188 manual post-processing. In the former case, the material coming out of the extruder was bent around

189 a stainless steel tool ($\varnothing = 15$ mm) and then removed after 2 min of cooling. In the latter case, the
190 extruded material was wrapped around a stainless steel tool ($\varnothing = 6$ mm), purposely developed with a
191 groove of the helix to be obtained (distance between adjacent turns = 5 mm), and then removed after
192 the same cooling time. Immediately after production, I-, U- and helix-shaped samples were packed
193 in heat seal alufoil moisture barrier bags.

194 Filaments for FDM were prepared under analogous process conditions by extruding the same
195 polymeric formulations through a custom-made aluminum circular die ($\varnothing = 1.80$ mm), as reported in
196 (Melocchi et al., 2016). Extruded rods were manually pulled and forced to pass through a caliper
197 connected with the extruder and set at 1.80 mm. This was required to counteract possible swelling
198 phenomena of the extruded rods and calibrate the relevant diameter, thus enhancing the yield of final
199 product compliant with the specifications set, *i.e.* 1.75 ± 0.05 mm. After production and cooling,
200 filament diameter was verified every 5 cm in length, and portions out of specifications were discarded.
201 Indeed, filaments with diameter greater than 1.80 mm were unsuitable for printing.

202

203 2.2.2.2 3D printing

204 FDM was performed by a Kloner3D 240[®] Twin (Kloner3D, I) printer equipped with 0.4 mm nozzle
205 (infill = 100%, layer height = 0.10 mm, printing speed = 23 mm/s, separation gap for raft and supports
206 = 0.5 mm), using computer-aided design (CAD) files purposely developed. Items were designed using
207 Autodesk[®] Autocad[®] 2016 software version 14.0 (Autodesk Inc., US-CA), saved in .stl format and
208 imported to the 3D printer software (Simplify 3D, I). A further software (Netfab, I) was employed
209 when the mesh number of the digital model needed to be increased, *i.e.* in the case of samples
210 comprising curvatures.

211 Portions 25 cm long of the in-house prepared filaments were used. Printing temperature was set as
212 reported in Table 1.

213

214

Table 1: HME and FDM process conditions

Material	HME			FDM
	T (°C)	Screw speed (rpm)	Torque (N·cm)	T (°C)
PVA05	200	100	190	200
PVA05GLY	170	100	100	180
PVA18GLY	200	100	220	n.d.*
PVA05GLY-CFF	175	100	120	185

215 *n.d. = not determined because of unfeasible manufacturing

216

217 2.2.3 Thermo-mechanical characterization

218 Samples cut from I-shaped items fabricated by HME and FDM, were subjected to **differential**
 219 **scanning calorimetry (DSC)** and **dynamic-mechanical thermal analysis (DMTA)**.

220 DSC analyses were performed by DSC Q100 (TA Instruments, US-DE; **n = 1**), using nitrogen as a
 221 purge gas (70 mL/min). Indium was used as a calibration standard. Samples of about 10 mg were
 222 heated in aluminum crucibles from -50 °C to 240 °C, maintained at this temperature for 1 min, cooled
 223 down to -50 °C and reheated up to 240 °C. Both heating and cooling steps were run at 10 °C/min.
 224 Additional DSC tests were carried out with wet samples, maintained in distilled water for 30 min,
 225 and equilibrated under ambient conditions overnight (final water content of about 8-10% evaluated
 226 by thermogravimetric analysis).

227 DMTA tests were performed by a Q800 TA Instruments analyzer (TA Instruments, US-DE; **n = 1**),
 228 in displacement-controlled tensile mode, on \approx 15 mm long specimens. The experiments were carried
 229 out at 1 Hz, with an applied displacement amplitude of 10 μ m, from -50 °C to a maximum temperature
 230 equal to 100 °C / 120 °C, at a heating rate of 3 °C/min.

231

232 2.2.4 Water-induced shape memory experiments

233 The shape memory test consisted of two different phases, *i*) programming of the temporary shape and
 234 *ii*) recovery of the original shape (Figure 2). The programming step was performed as follows.

235 - Heating of the sample up to the deformation temperature ($T_{\text{def}} \approx T_g + 35 \text{ }^\circ\text{C}$, where T_g indicates the
236 material glass transition temperature measured by DSC).

237 - Deformation, by means of specially designed tools, of the sample maintained at T_{def} . Samples having
238 original U- or helix-shape were deformed to take on programmed temporary I-shape. Conversely, I-
239 shaped samples were deformed to take on programmed temporary U-shape.

240 - Cooling of the sample in the fixed temporary shape below T_g . In case of plasticized PVAs, showing
241 relatively low T_g , after deformation the samples were kept in a freezer at $-20 \text{ }^\circ\text{C}$ in order to avoid
242 early recovery.

243 Recovery of the original shape was obtained following immersion of the deformed samples into 100
244 mL of unstirred distilled water. The experiment was carried out both at room temperature and at 37
245 $\pm 0.5 \text{ }^\circ\text{C}$, by using a thermoregulated bath. The recovery process was monitored using digital cameras
246 ($n = 1$, Nikon D700 18-105 VR Kit, AF-S DX NIKKOR 18-105 mm f/3.5-5.6G ED VR, J and GoPro
247 Hero Session, US-CA).

248 In case of originally I- or U- shaped samples, photographs acquired were processed by means of a
249 specific software (ImageJ, US-MD) to measure the variation of the angle between the two arms (α)
250 occurring during the recovery. Recovery index (RI) versus time curves were then built, with RI
251 calculated as follows:

252 - for specimens with original I-shape

$$253 \quad \text{RI} = \frac{\alpha - \alpha_p}{\pi - \alpha_p} \quad \text{Eq. (1)}$$

254 - for specimens with original U-shape

$$255 \quad \text{RI} = 1 - \frac{\alpha}{\alpha_p} \quad \text{Eq. (2)}$$

256 where α_p is the angle obtained in the programming phase (angles in rad).

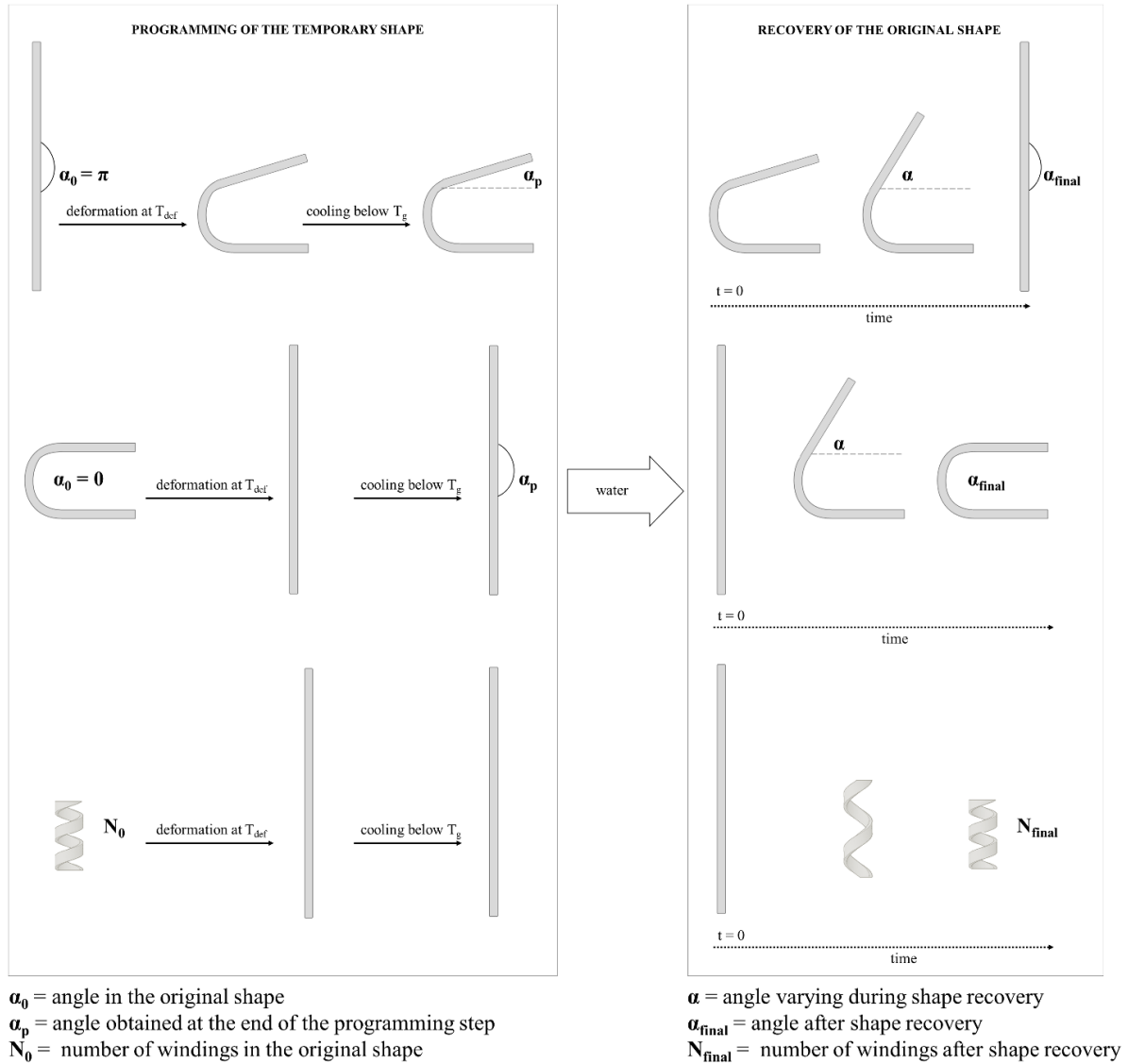
257 The time ($t_{\text{RI final}}$) to reach final RI (RI_{final}), *i.e.* the RI value calculated based on measurement after
258 which no more changes in α were observed, was also recorded.

259 For specimens with original helix-shape, only the RI_{final} was considered, being calculated as follows:

260 $RI_{\text{final}} = \frac{N_{\text{fin}}}{N_0}$ Eq. (3)

261 where N_{final} and N_0 represent the number of windings at the end of recovery and before programming,
 262 respectively.

263



264

265 **Figure 2:** outline of the experiments performed to evaluate the water-induced shape memory
 266 response.
 267

268 2.2.5 Evaluation of fluid uptake and residual dry mass

269 Extruded and printed samples having original I-shape ($n = 3$) were characterized in terms of fluid
 270 uptake and residual dry mass over 4 h of immersion in unstirred simulated urine fluid (400 mL) kept

271 at 37 ± 0.5 °C prepared as indicated in (Sherif et al., 2018). Each specimen was laid on a stainless
272 steel net ($w = 2.5$ cm, $h = 7$ cm, mesh = 1.5 mm) before immersion and then withdrawn after
273 predetermined time periods, gently blotted and weighed. Final dry masses were also determined after
274 maintaining samples in an oven at 40 °C for 24 h. Two parameters were calculated, the percentage
275 **fluid uptake (FU) and the percentage residual dry mass (RDM)**, according to the following equations:

$$276 \quad FU(\%) = \left[\frac{(W_m - W_d)}{W_m} \right] \times 100 \quad \text{Eq. (4)}$$

277 where W_m is the mass of the wet sample on withdrawal and W_d is the mass of the sample after drying;

278

$$279 \quad RDM(\%) = 1 - \left[\frac{(W_i - W_d)}{W_i} \right] \times 100 \quad \text{Eq. (5)}$$

280 where W_i is the initial mass of the sample.

281

282 2.2.6 Evaluation of release performance

283 Tracer-containing extruded and printed samples were tested for release using a USP38 dissolution
284 apparatus 2 (10 rpm, 37 ± 0.5 °C; Distek, CH; $n = 3$). 400 mL of simulated urinary fluid were used
285 as the dissolution medium. Fluid samples were withdrawn at specific time points and assayed
286 spectrophotometrically ($\lambda = 206$ nm). By linear interpolation of the release data immediately before
287 and after the time point of interest, times to 10% and 90% release ($t_{10\%}$ and $t_{90\%}$, respectively) were
288 calculated.

289 During the release test, photographs of samples were taken every 5 s (GoPro Hero Session, US-CA).

290

291 3. Results and Discussion

292 The temporary shape of a retentive intravesical delivery system should be such as to allow
293 administration through a catheter without any constraints (*e.g.* straight bars with limited diameter and
294 indefinite length). On the other hand, recovery of the original shape, designed to promote retention
295 within the bladder for a pre-determined period of time (from few hours up to several days) without

296 damaging its walls, should spontaneously take place *in situ* as a result of interaction with biological
297 fluids. If water soluble SMPs are chosen as main components of the delivery system, no invasive
298 procedure would ultimately be needed for the relevant removal.

299

300 3.1 Design and fabrication of specimens

301 The experimental work was aimed at attaining specimens showing water-induced shape shifting
302 phenomena representative of each stage of performance for the retentive intravesical delivery
303 platform proposed. For this purpose, hot-processing techniques, namely HME and FDM, were
304 employed. FDM has recently been demonstrated to be a versatile manufacturing process for
305 fabrication of drug delivery systems having complex geometries and composition, such as orally
306 administered dosage forms (*e.g.* tablets, matrices, capsules, hollow and multilayer systems), implants
307 and inserts (Genina et al, 2017, Goole and Amighi, 2016, Goyanes et al., 2015, Maroni et al., 2017,
308 Melocchi et al., 2015a, 2018, Okwuosa et al., 2017, Sandler and Preis, 2016, Tagami et al., 2018,
309 Zema et al, 2016). In the particular field of intravesical delivery, which FDM has not been applied to
310 so far, this 3D printing technique would grant the possibility of personalizing the pharmacological
311 therapy in terms of type and dose of conveyed drugs, possible co-administration scheme (fixed drug
312 combinations or extemporaneous compositions), and achievable release kinetics. With regard to HME,
313 not only would it be viable for the device fabrication, but also is necessarily associated with FDM
314 processing as it provides the filaments required for printer feeding.

315 Among polymers exhibiting water-induced shape memory response and good hot-processability,
316 swellable/erodible ones, able to interact with aqueous fluids ultimately dissolving/eroding, appeared
317 especially advantageous as main components for the delivery system. Indeed, such materials undergo
318 a glass-rubber transition when in contact with biological fluids with formation of a gel, the
319 dissolution/erosion behavior of which depends on the relevant viscosity and, therefore, on the
320 polymer molecular weight. Particularly, PVA was selected based on both the experience gained on
321 relevant processing *via* HME and FDM as well as the review of preliminary literature findings on the

322 exhibited water-driven shape memory ability, which relies on its semi-crystalline nature or may be
323 obtained by crosslinking (De Jaeghere et al., 2015, Fang et al., 2017, Melocchi et al., 2015b, 2016,
324 Qi et al., 2014). With respect to SMPs already proposed for drug delivery purposes, mainly including
325 newly synthesized crosslinked polymers wanting regulatory approval, the PVA selected offers the
326 advantage of a long-established use and safety profile (Nagahama et al., 2009, Neffe et al., 2009,
327 Wischke et al, 2009, Wischke and Lendlein 2010). In addition, being available in different molecular
328 weights, it was expected to be a versatile material that would allow for a range of diversified release
329 rates of the active ingredient conveyed and bladder retention times of the system.

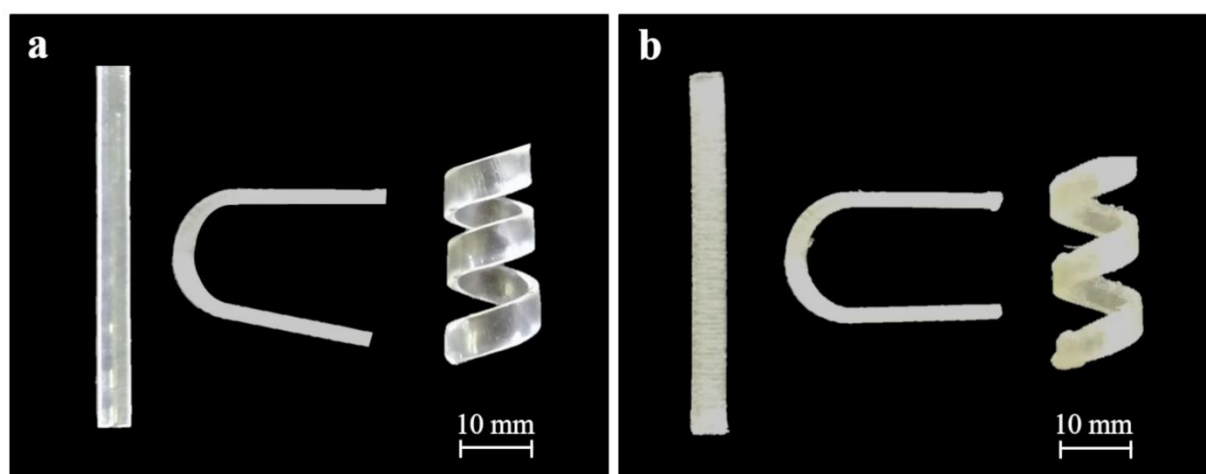
330 Different molecular weights of PVAs, either unplasticized or in admixture with a plasticizer and/or
331 tracer, were used. In order to broaden the scope of information achievable in terms of process and
332 performance, the specimens based on these formulations were conceived in three geometries, having
333 different extent of complexity, either mimicking the original (*i.e.* enabling bladder retention) or the
334 temporary (*i.e.* enabling administration) shape of the device: a U-shaped item, a helix, as a possible
335 evolution of the U-shape, and a simple straight bar (I-shape). The latter shape was chosen as a
336 prototypical screening tool on account of the expected ease of fabrication, while the helix shape was
337 considered of particular interest in view of intravesical application as it combines several advantages
338 and a rather simple design. As compared with the U-shape, helical geometry could not only take on
339 a temporary bar-like shape suitable for administration and then recover the original retentive
340 configuration, but also be expected to have improved bladder retention, thanks to their numerous
341 windings, and enhanced patient compliance. Indeed, a helix might behave like a spring that undergoes
342 compression from resting position and shortens its natural length, thereby withstanding possible
343 mechanical stresses, deriving from muscle contraction during urination, and limiting discomfort. If
344 further improvement of the helical geometry were pursued, the presence of any sharp tip might be
345 overcome to reduce the potential for damaging the urothelium.

346 Originally I-, U- and helix-shaped samples were fabricated by FDM starting from in-house extruded
347 filaments. Specimens having such designs were also fabricated by HME for comparison purposes and

348 were thus used as a reference to design the virtual models for FDM. By way of example, Figure 3
349 shows photographs of the extruded and printed samples based on plasticized PVA05. Notably,
350 materials being extruded have to undergo bending and coiling before cooling to reach final original
351 shapes other than straight ones, thus involving purposely-developed tools and attentive process
352 design. Conversely, items having relatively complex geometries (*e.g.* U- and helix-shape) could
353 directly be fabricated by 3D printing. Revision of CAD files was needed to counteract possible
354 expansion phenomena encountered with the polymeric formulations in use following preliminary
355 printing trials. Indeed, by calculating a correction coefficient, as described in (Melocchi et al, 2015a),
356 printed items matching the dimensions of those prepared by HME were obtained. In addition, for
357 samples comprising curvatures (*i.e.* originally U-shaped and helix-shaped specimens), the mesh
358 number, *i.e.* a collection of vertices, edges and faces used to describe the shape of a tridimensional
359 object, had to be increased in the virtual model in order to improve the resolution thus obtaining a
360 smoother surface. FDM was performed by means of a 3D printer characterized by two arms working
361 independently, which enabled contemporaneous fabrication of different parts thus reducing the
362 overall printing time. The presence of a fixed build plate allowed to overcome manual calibration
363 issues and also limited the exposure of the object in fabrication to uncontrolled airflow, known to
364 hinder uniform cooling thereby impacting on product mechanical properties (*e.g.* reduced stiffness,
365 layer detachment in the area subjected to greater cooling). Items were fabricated in the presence of a
366 raft, because this turned out to increase adhesion of first printed layers to the build plate. Printing of
367 helix-shaped items also required the use of supports between each winding to avoid collapsing during
368 vertical growth. A separation gap of 0.5 mm was set between the object and the raft as well as supports
369 to make them easily removable without damage. Printing speed was kept low (23 mm/s) to enhance
370 accuracy and avoid dragging of latest layered material, which may cause detachment of the item in
371 fabrication from the build plate. Under these conditions, PVA05-based formulations were
372 successfully printed without technical issues at temperatures established on the basis of their thermal
373 behavior. As expected, the presence of the plasticizer resulted in improved printing and reduced

374 number of failures. Notably, the obtained helical-samples, subjected to manual compression, were
375 shown to behave like a spring, *i.e.* shorten in length when stressed and then return to the initial
376 position after stress removal. In spite of the overall actions taken to make the process feasible, it was
377 not possible to print any item starting from PVA18, either unplasticized or in admixture with **GLY**.
378 Indeed, because the pressure needed for material extrusion during the 3D process is only exerted by
379 the mass of the filament being loaded, the melt viscosity of such polymer was too high to enable its
380 flow through the available nozzle. While increasing the printing temperature was expected to reduce
381 the polymer viscosity, such an adjustment turned out not to be viable as browning of the material was
382 observed. On the other hand, HME was successfully carried out with all the PVA formulations under
383 investigation, except for PVA18 in the absence of plasticizer because torque values exceeding the
384 maximum allowed by the equipment in use would have been needed.

385



386

387

Figure 3: photographs of originally I-, U- and helix-shaped specimens based on PVA05GLY
388 obtained by a) HME and b) FDM.
389

389

390 3.2 Shape memory response

391 A basic experimental screening was carried out on I-shaped specimens obtained by HME and FDM
392 in order to determine how the thermo-mechanical properties of samples may lead to their shape
393 memory. In particular, as the temperature required to activate the shape transformation strictly
394 depends on the material glass transition temperature, DSC analyses were initially performed. Indeed,

395 shape shifting phenomena depend on amorphous regions of the polymer gaining mobility when T_g is
396 reached, while permanent shape could be supported by crystalline domains, which would undergo
397 melting at a higher temperature thus acting as net points (Fang et al, 2017). Therefore, evaluating
398 how T_g is affected by the polymer grade, the presence of plasticizer and the interaction with water is
399 of utmost importance because the temporary shape *i*) must be programmed at $T_{def} > T_g$ (in the present
400 case $T_{def} \approx T_g + 35 \text{ }^\circ\text{C}$), *ii*) can be preserved keeping the material at $T < T_g$ and *iii*) is reversed to the
401 original shape at $T > T_g$. In this specific case, shape recovery phenomena should take place at $37 \text{ }^\circ\text{C}$.
402 Because shape recovery is activated at temperatures above T_g , any change in such a property is
403 expected to be highlighted in the shape memory experiments. By DMTA, the evolution of material
404 stiffness was described, and in particular storage modulus was measured below **room temperature**
405 (T_{room}) and at T_{def} , corresponding to sample stiffness before and after recovery, respectively.

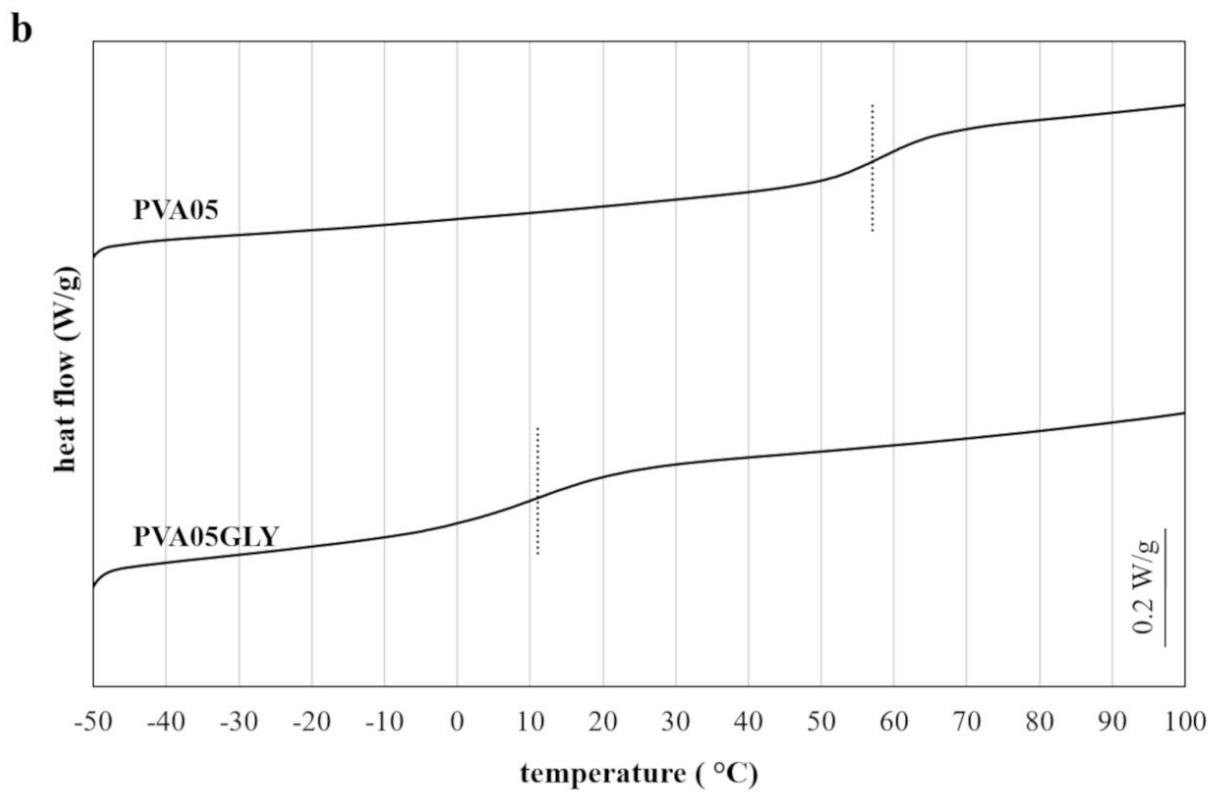
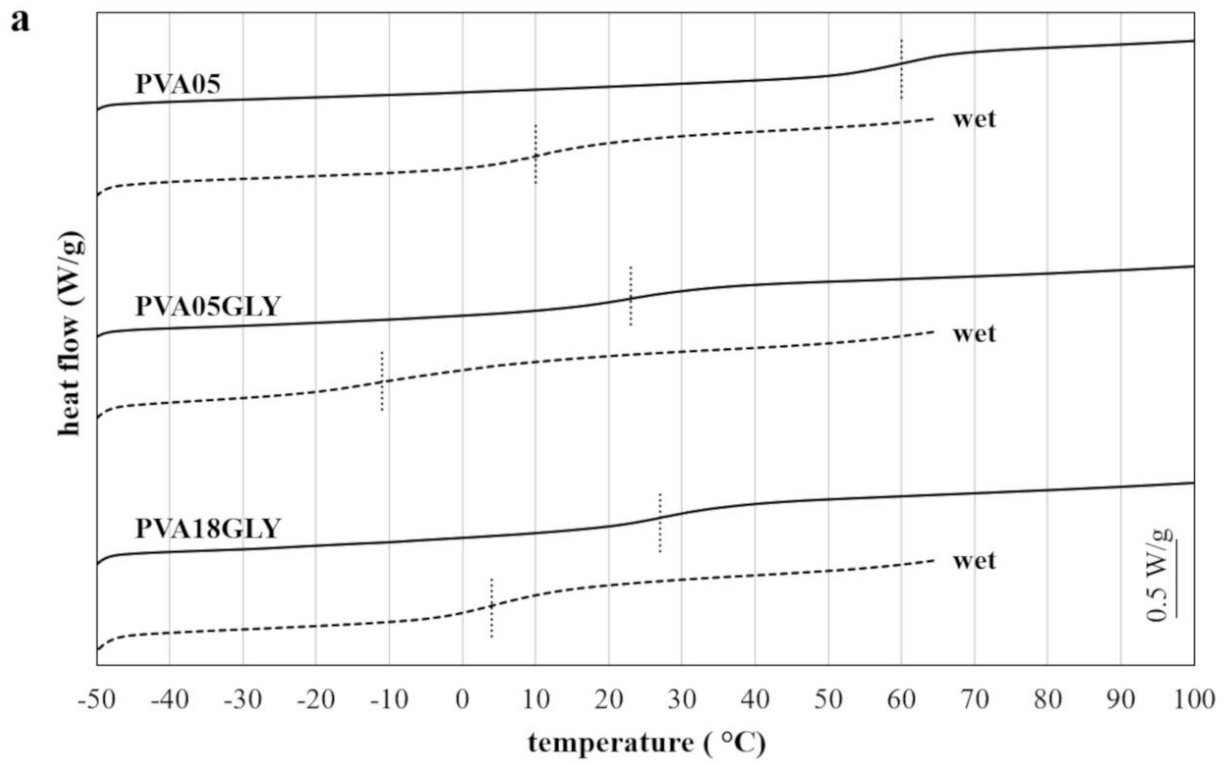
406

407 3.2.1 DSC experiments

408 DSC thermograms are reported in Figure 4, choosing the second scan since it provided T_g values
409 similar to those of the first one but easier to read. These curves displayed a regular shape, *i.e.* a well-
410 defined inflection point corresponding to the material T_g , and no other exo-/endo-thermal signals. T_g
411 values obtained from these thermograms are reported in Table 2: minor differences in T_g measured
412 for extruded and printed specimens were observed.

413 The plasticization effect of **GLY** turned out evident for PVA05, as a decrease of $37 \text{ }^\circ\text{C}$ and $46 \text{ }^\circ\text{C}$ in
414 T_g was noticed with PVA05GLY-based samples obtained by HME and FDM, respectively. **Such an**
415 **effect was attributed to the ability of the plasticizer to modify the 3D organization of the polymer**
416 **matrix (Mohsin et al., 2011). In fact, due to its low-molecular weight and hydroxyl groups, GLY is**
417 **known to lead to the formation of polymer-plasticizer hydrogen bonds to the detriment of interactions**
418 **among polymer chains, thus reducing the intermolecular attraction forces and increasing the**
419 **macromolecule mobility at temperatures below those at which the neat polymer undergoes transition.**

420 In the case of wet samples, it was evident that also water taken up acted as a plasticizer for PVA,
421 reasonably by weakening intra- and inter-molecular hydrogen bonds and increasing mobility of
422 macromolecular chains (Figure 4a, Table 2). Indeed, progressive water absorption is known to
423 concomitantly induce a decrease in the polymer T_g below room temperature until an equilibrium is
424 reached. Particularly, the most marked decrease was recorded in the case of the wet as compared with
425 dry PVA05 sample. The observed plasticization effect of water, allowing macromolecules to gain
426 mobility, would enable activation of the shape shifting process at room temperature and below, which
427 is the basis for the water-induced shape memory response.



428

429 **Figure 4:** DSC thermograms (in the T_g region) from originally I-shaped specimens obtained by a)
 430 HME and b) FDM. Dotted vertical bars indicate T_g .

431

432

433

434

435 **Table 2:** T_g from DSC analyses, for originally I-shaped specimens obtained by HME and FDM.
436 Data in brackets refer to wet samples
437

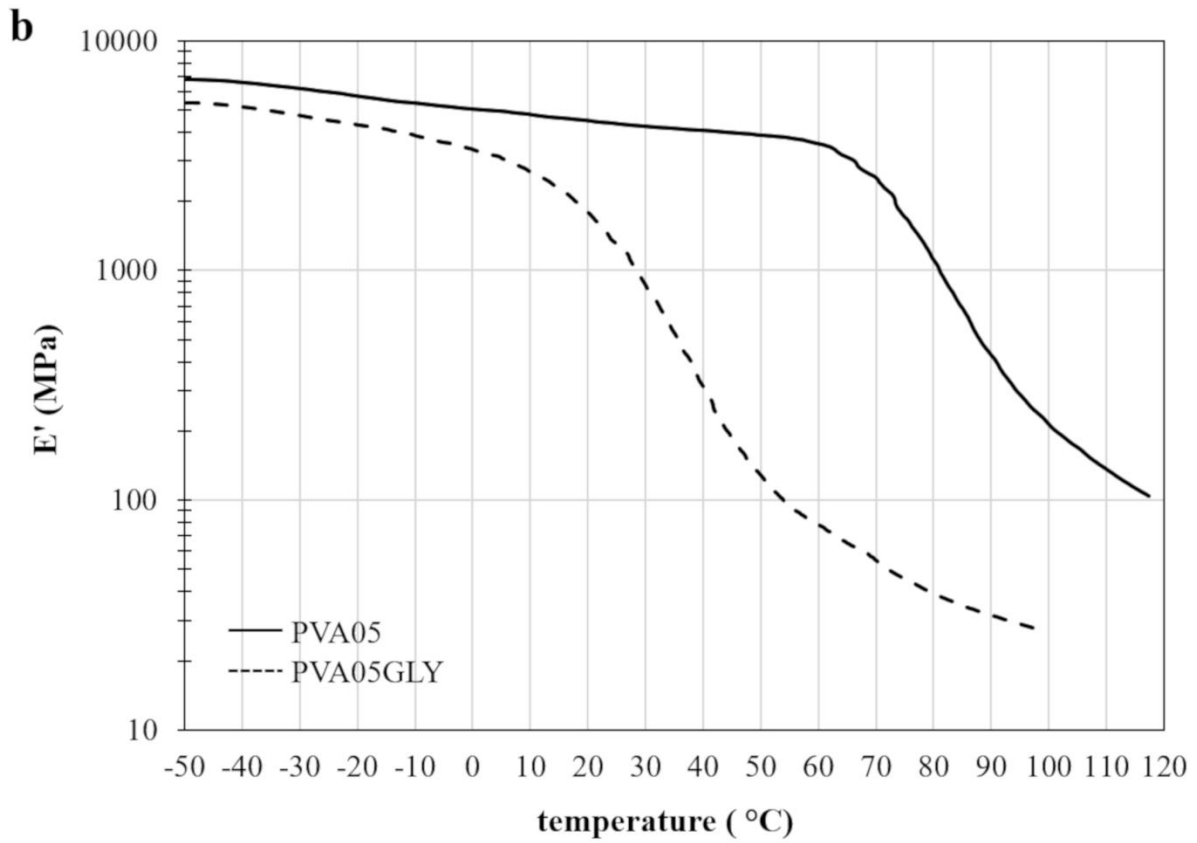
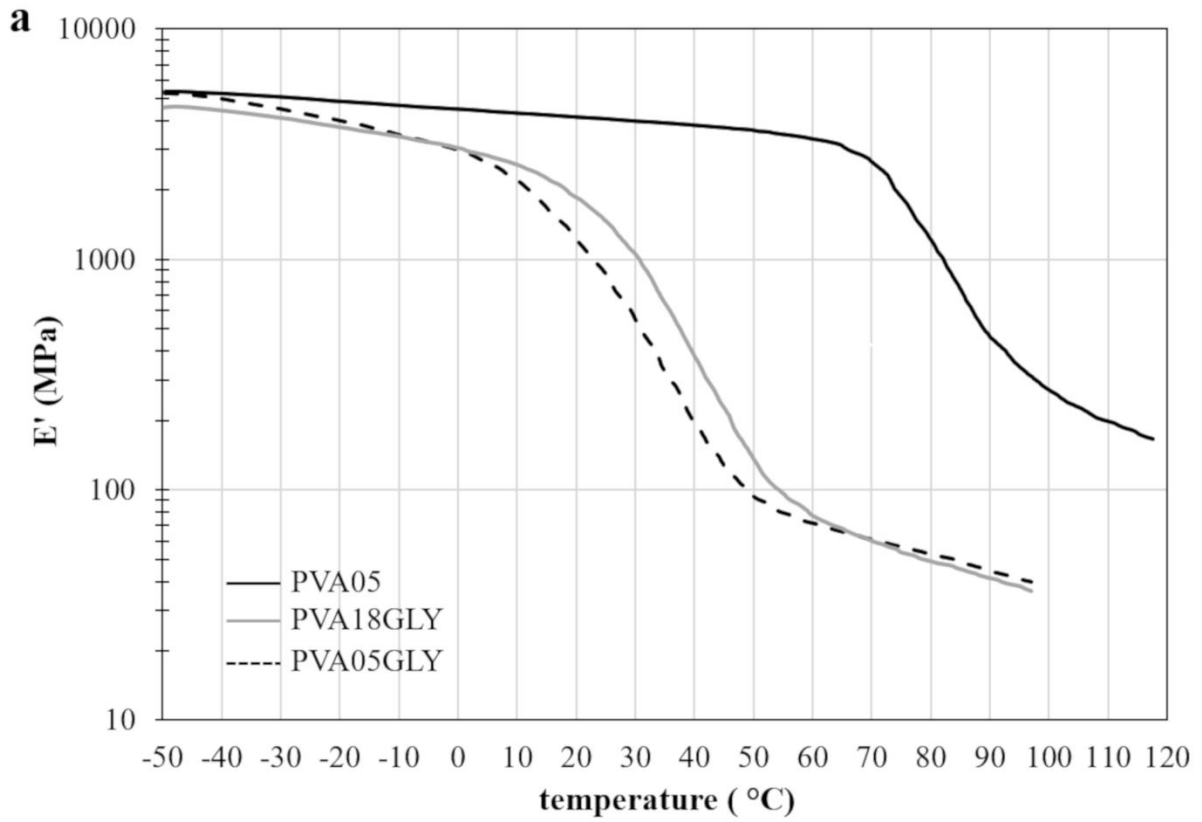
	T_g ($^{\circ}\text{C}$)	
	HME	FDM
PVA05	60 (10)	57
PVA05GLY	23 (-11)	11
PVA18GLY	27 (4)	n.a.*

438 * n.a. = non-available sample because of unfeasible manufacturing

439

440 3.2.2 DMTA experiments

441 Figure 5 shows the **storage modulus (E')** vs temperature curves obtained from extruded and printed
442 specimens subjected to DMTA.



443

444 **Figure 5:** E' vs temperature curves from originally I-shaped specimens obtained by a) HME and b)
 445 FDM.
 446

447 The plasticization effect induced by **GLY**, previously observed in DSC thermograms, was confirmed
 448 by DMTA data. **Indeed, the reduced extent of interaction among PVA chains brought about by the**
 449 **addition of plasticizer resulted in a decrease in the sample stiffness, irrespective of the manufacturing**
 450 **technique considered. A decrease in T_g for GLY-containing specimens was confirmed by shifting of**
 451 **E' curves towards lower temperatures.** E' traces also provided an indication of the stiffness of the
 452 material below and across the transition region. Table 3 reports E' values determined both at room
 453 temperature (E'_{Room}) and at T_{def} (E'_{Tdef}), at which the material showed a rubbery behavior, as well as
 454 the relevant percentage difference ($\Delta E'$), defined as:

$$455 \quad \Delta E'(\%) = \frac{E'_{\text{Room}} - E'_{\text{Tdef}}}{E'_{\text{Room}}} \times 100 \quad \text{Eq. (6)}$$

456 These values were chosen since E'_{Room} would be representative of the stiffness of samples in their
 457 original shape, E'_{Tdef} would be an estimation of such a characteristic right after the shape memory
 458 transition, while $\Delta E'$ would represent the overall stiffness change during the transition. E'_{Tdef} and $\Delta E'$
 459 may overestimate and underestimate, respectively, stiffness and overall change in stiffness, since it
 460 is known that water absorption, and eventually polymer dissolution, would lead to a relevant decrease.

461

462 **Table 3:** E'_{Room} , E'_{Tdef} and $\Delta E'$ from originally I-shaped specimens obtained by HME and FDM

463

	E'_{Room} (MPa)		E'_{Tdef} (MPa)		$\Delta E'$ (%)	
	HME	FDM	HME	FDM	HME	FDM
PVA05	4060	4330	440	410	89	90
PVA05GLY	830	2750	70	120	92	96
PVA18GLY	1420	n.a.*	80	n.a.*	94	n.a.*

464 * n.a. = non-available sample because of unfeasible manufacturing

465

466 Irrespective of the manufacturing technique employed, PVA05 specimens displayed a stiff behavior
 467 at T_{room} , the storage modulus decreasing of one order of magnitude at T_{def} with an overall stiffness
 468 change of about 90%. Not only the PVA05GLY but also PVA18GLY samples exhibited, because of
 469 the presence of **GLY**, lower E'_{Room} and E'_{Tdef} , and a slightly higher overall variation (92-96%). The

470 higher stiffness shown at T_{room} by printed specimens with respect to extruded ones might be ascribed
471 to processing.

472 In general, the drop of E' indicates the occurrence of a relaxation process that, for these materials,
473 could be ascribed to glass transition of PVA (Chartoff et al, 2009). In support of the DSC data, T_g
474 was also evaluated by DMTA, confirming minor differences, associated with the technique employed
475 for sample manufacturing, as observed by DSC. Indeed, for a given material and specimen
476 preparation method, a difference between transition temperatures determined by DSC and by DMTA,
477 with the latter being systematically higher than the former, is expected and intrinsically related to the
478 differences between the two experimental techniques and corresponding testing parameters, such as
479 heating rate and frequency. Because transition temperatures coming from DMTA exhibit testing
480 frequency dependence, T_g values obtained by DSC were used for assessment of T_{def} in the shape
481 memory experiments.

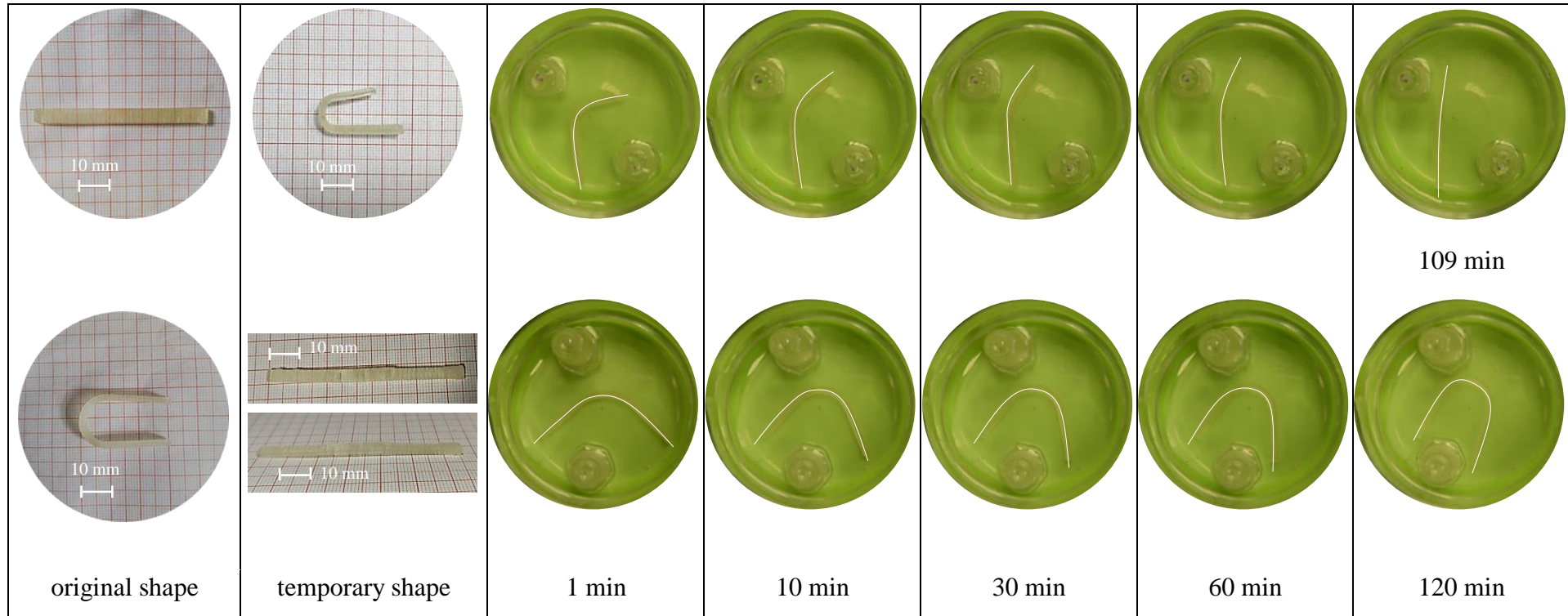
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483 3.2.3 Shape recovery experiments

484 The water-induced shape recovery process was studied in unstirred distilled water at room
485 temperature, by monitoring evolution of the shape of extruded and printed samples from the
486 temporary one. By analyzing photographs taken at successive time points, RI was calculated to
487 describe the shape recovery process. By way of example, images of printed PVA05GLY specimens
488 having different original shapes are collected in Table 4.

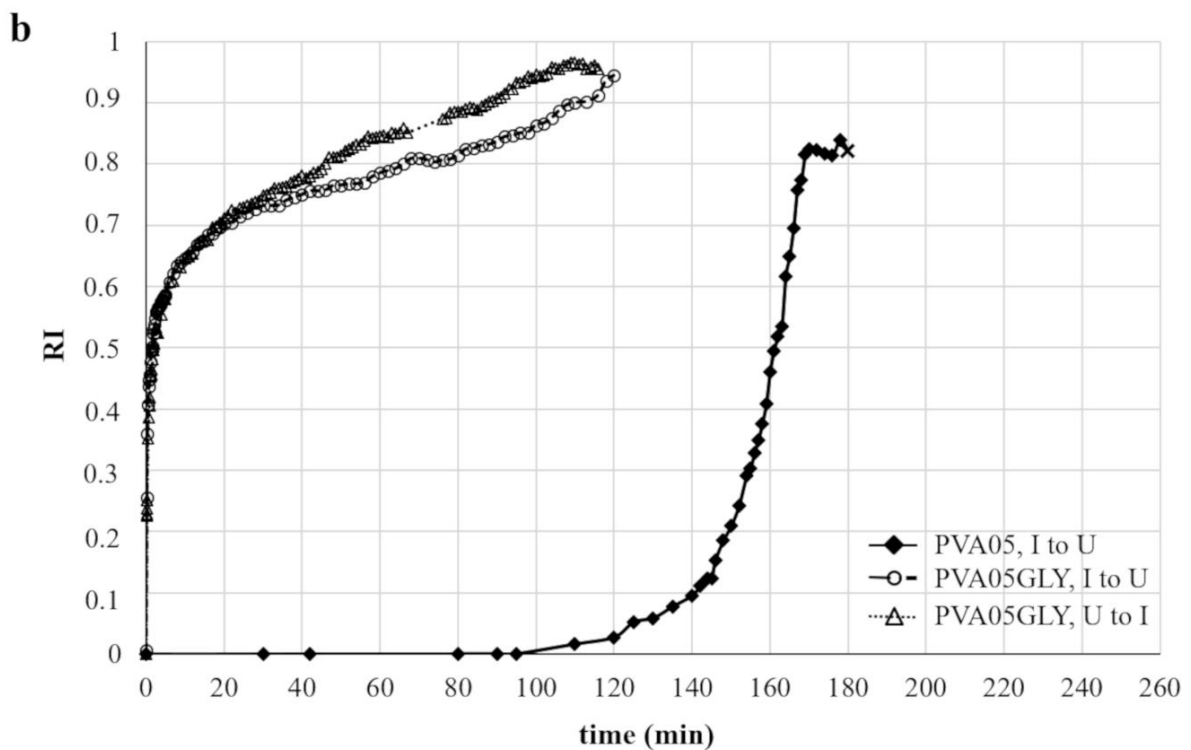
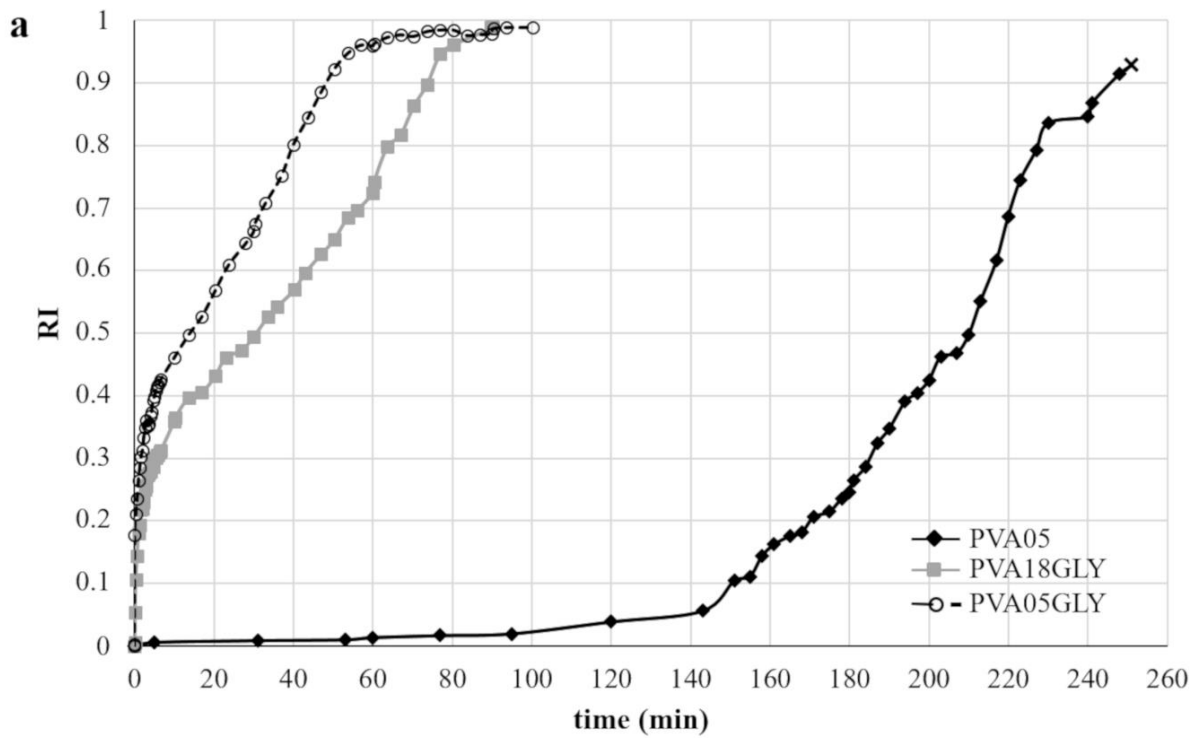
489

490 **Table 4:** photographs acquired during shape recovery experiments (room temperature) of PVA05GLY specimens having original I- and U-shape
 491 obtained by FDM. A solid line is superimposed to highlight the recovery process
 492



493

494 The recovery ability observed for a very simple original shape (*i.e.* I-shaped specimen programmed
495 to take on temporary U-shape) was also shown by samples having an original U-shape (programmed
496 to take on temporary I-shape) and comparable recovery times were found in both cases, irrespective
497 of geometry. A shape-shifting effect similar to that exhibited by printed PVA05GLY samples was
498 observed for the other formulations examined. An almost full recovery of the original shape was
499 obtained from specimens having all geometries under investigation. The recovery process was also
500 monitored over time and α was measured at successive time points to calculate the corresponding RI
501 values. Recovery curves from selected extruded and printed samples with different original shapes
502 are reported in Figure 6. With PVA05 samples, determination of RI in the final stage of the recovery
503 process was impaired by concurrent polymer dissolution causing distortion of the specimens, which
504 impaired the assessment of their shape evolution. In such cases, measurements had to be interrupted,
505 and this was highlighted in the curves by marking the last RI value acquired.



506

507 **Figure 6:** RI vs time curves from a) originally I-shaped specimens of all compositions obtained by
 508 HME and b) originally I- and U-shaped PVA05-based specimens obtained by FDM, tested at room
 509 temperature (x indicates the last datum acquired before measurements were impaired by the
 510 polymer dissolving).
 511

512 For samples manufactured by HME, the addition of **GLY** to PVA05 modified the recovery process
513 kinetics (Figure 6a). This is consistent with previous reports showing the effect of plasticizer on the
514 shape memory response of semi-crystalline polymers (Cai et al., 2017). With unplasticized PVA05,
515 recovery showed an initial induction phase followed by a high rate phase (about 120 min long). By
516 contrast, with PVA05GLY the process started with a high rate without any induction phase and the
517 overall duration of recovery was reduced. These differences may be related to the fact that for
518 PVA05GLY, having T_g below the recovery test temperature, the recovery process would be a
519 combination of water- and temperature-induced shape memory effects, whereas for the unplasticized
520 polymer, having T_g above the test temperature of approximately 30 ° C, recovery would result from
521 water-induced shape memory only. Moreover, because of the greater free volume associated with the
522 lower T_g , water diffusion phenomenon may be faster with the plasticized polymer, thus resulting in a
523 faster activation of the shape memory effect. As regards PVA18, HME was feasible with the
524 formulation containing **GLY** only, and the resulting sample exhibited a similar recovery pattern as
525 compared with the PVA05GLY one, although the rate of the process was lower after the first few
526 minutes of testing. The influence of molecular weight of the polymer on the relevant shape shifting
527 phenomena would deserve further investigation, also considering literature findings mainly focused
528 on its impact on recovery index (Chen et al., 2007, Petisco-Ferrero et al., 2016).

529 In Figure 6b, it can be observed that the recovery curve of the printed PVA05 specimen showed an
530 analogous induction phase, of approximately 2 h, with respect to the extruded sample having the same
531 composition. However, the recovery rate in the subsequent phase turned out higher for the specimen
532 obtained by FDM. The printed vs extruded PVA05GLY specimens were characterized by much faster
533 initial recovery followed by a decrease in the process rate after some minutes from the beginning of
534 the test, regardless of their original shape. Such differences in the initial recovery rate might be related
535 to the different surface porosity/roughness of specimens fabricated by HME and FDM. Although
536 specimens of comparable dimensions were prepared by the two techniques, the effective
537 surface/volume ratio that governs water absorption kinetics is likely to be higher for printed than

538 extruded specimens due to a more porous structure resulting from the additive manufacturing process.
 539 The subsequent decrease in recovery rate of printed items, together with a less marked difference in
 540 the time needed for complete recovery observed with plasticized *vs* unplasticized samples, may be
 541 suggestive of the inherent layered nature, which would be brought out by the contact with water. It
 542 could be hypothesized that the various layers may not swell jointly following progressive water
 543 penetration. By contrast, extruded items would most likely be expected to behave as a continuous
 544 matrix. However, such an aspect is little known and is worth being explored, because in-depth studies
 545 comparing the water-induced shape memory response of extruded and printed items have not been
 546 reported in the scientific literature. An investigation into the possible differences in the temperature-
 547 induced shape memory behavior of items obtained starting from poly(ethylene-co-methacrylic acid)
 548 either by FDM or compression molding, a technique well-known for producing non-porous items,
 549 has so far been reported (Zhao et al., 2017).
 550 Recovery studies were also carried out under body temperature conditions. Table 5 summarizes RI_{final}
 551 values obtained and corresponding $t_{RI_{\text{final}}}$, collected at room temperature and 37 °C from extruded and
 552 printed specimens having original I-shape.

553

554 **Table 5:** RI_{final} values and corresponding $t_{RI_{\text{final}}}$ from specimens having original I-shape tested at
 555 room temperature and 37 °C

		Room temperature		37 °C	
		RI_{final}	$t_{RI_{\text{final}}}$ (min)	RI_{final}	$t_{RI_{\text{final}}}$ (min)
HME	PVA05	0.93 ^a	251 ^a	0.97	146
	PVA05GLY	0.99	100	0.86	28
	PVA18GLY	0.99 ^a	90 ^a	0.92 ^a	55 ^a
FDM	PVA05	0.82 ^a	180 ^a	n.d.	n.d.
	PVA05GLY	0.97	109	0.88 ^a	26 ^a

556 ^a determination hindered by dissolving of the polymer with possible distortion of the
 557 specimen

558 n.d. = not determined because of pronounced distortion of the specimen

559

560 Generally high RI_{final} was shown by both extruded and printed specimens, with lower values for
 561 PVA05-based formulations. Because shape recovery and polymer dissolution occur concomitantly,

562 RI_{final} could hardly be determined when the rate of shape recovery was lower than that of dissolution,
563 thus leading to considerably reduced size or changes in consistency of the sample. In the case of the
564 printed PVA05 specimen, it was not even possible to determine RI_{final} because of dissolution-driven
565 distortion that was ascribed to the reduced gel viscosity and sample stiffness due to the high extent of
566 hydration reached, close to the dissolution threshold. At both temperatures, the presence of GLY
567 accelerated the recovery process, with up to a four-fold decrease in $t_{RI_{\text{final}}}$ at 37 °C for PVA05GLY
568 specimens. Because the T_g was by far lower than the test temperature, such a marked acceleration of
569 recovery may have resulted from a combination of water- and temperature-induced shape memory
570 effects. A reduction of $t_{RI_{\text{final}}}$ was observed for all formulations tested at 37 °C as compared with room
571 temperature, with extent of reduction of $t_{RI_{\text{final}}}$ consistent with that of T_g values, as could be expected
572 based on the increased mobility of the amorphous PVA domains. In the case of extruded specimens
573 containing plasticizer (PVA05GLY and PVA18GLY), the time needed for recovery turned out to be
574 affected by the polymer molecular weight at 37 °C.

575 The overall results confirmed that the use of originally straight bar-shaped samples as a screening
576 tool could be appropriate, and the information gathered may profitably be exploited in the design of
577 devices with more complex geometries

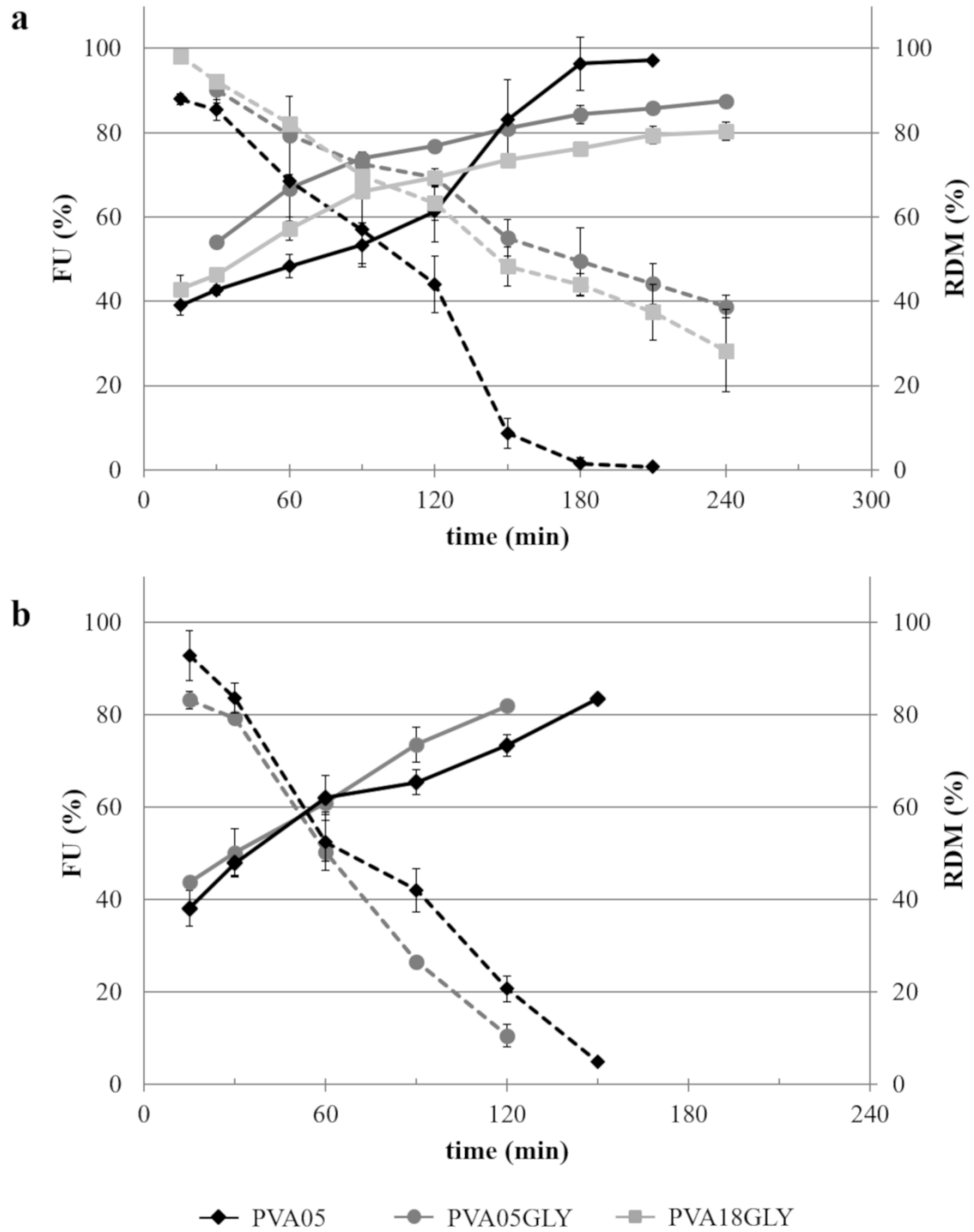
578

579 3.3 Fluid uptake and residual dry mass

580 Because thermo-mechanical properties and recovery of the original shape of samples was
581 demonstrated to be affected not only by temperature but also by their exposure to aqueous media, it
582 was deemed interesting to investigate the kinetics of biological fluid uptake. Concomitantly, the mass
583 loss behavior of the same specimens was studied over time. Indeed, the overall bladder retention time
584 of the device, the onset and time frame of shape shifting phenomena as well as its ability to control
585 the release of the conveyed drug would be related to the rate and extent of hydration and
586 erosion/dissolution of the polymeric formulation.

587 Extruded and printed specimens having original I-shape were thus evaluated for FU and RDM,
588 employing simulated urinary fluid kept at 37 ± 0.5 °C to mimic the environment in which the system
589 was supposed to perform.

590 From FU and RDM profiles, reported in Figure 7, it turned out evident that the rate of fluid uptake
591 was **by far** higher than that of mass loss. Indeed, approximately 40% of fluid taken up was reached
592 within the first 15 min of testing, irrespective of the formulation and manufacturing technique
593 considered. **In the case of extruded items, the rate of mass loss of PVA05GLY was greater than that**
594 **of PVA18GLY specimens. This could be explained on the basis of the different molecular weights**
595 **of the employed polymer, which is known to be associated with viscosity of the hydrated matrix thus**
596 **affecting the relevant rate of erosion/dissolution.** The addition of **GLY** to PVA05 slightly accelerated
597 the initial fluid uptake, which was evident especially in the case of extruded samples reasonably due
598 to their less porous structure **that could have hindered penetration of the aqueous medium. Because**
599 **of pronounced hygroscopicity, the plasticizer may have increased water affinity of specimens, thus**
600 **favoring absorption of the aqueous fluid (Mohsin et al., 2011). Indeed, the hydroxyl groups of GLY**
601 **would be able to establish hydrogen bonds with both water and polymer, thus increasing the**
602 **molecular mobility of the latter and the free volume in the samples. In the case of PVA05, the**
603 **threshold absorbed amount of aqueous medium needed for sufficient mobility of the polymer chains**
604 **to be acquired and dissolution to take place was therefore higher than with the plasticized formulation.**
605 Interestingly, the fluid uptake behavior of the specimens was consistent with the shape recovery
606 previously discussed. As expected, activation of shape shifting phenomena in **GLY**-containing
607 samples was especially rapid because the polymer T_g was not only decreased by the presence of
608 plasticizer but also by the relatively high extent of fluid taken up in the first minutes of testing.



609

610 **Figure 7:** average FU (solid lines) and RDM (dashed lines) curves from originally I-shaped
 611 specimens obtained by a) HME and b) FDM.

612

613 3.4 Evaluation of tracer-containing specimens

614 The potential of the PVA-based formulations under investigation for slowly releasing an active
 615 ingredient while undergoing prompt shape modifications was preliminarily evaluated using

616 specimens containing CFF as an analytical tracer. Specimens having original I-shape were initially
617 characterized for thermo-mechanical properties. A further decrease in T_g was found with respect to
618 the corresponding samples devoid of CFF ($T_g = 1\text{ }^\circ\text{C}$ vs $T_g = -3\text{ }^\circ\text{C}$ for extruded vs printed items),
619 which was already observed with a different thermoplastic polymer (Burgess et al., 2015). Moreover,
620 the printed and extruded tracer-containing specimens showed comparable stiffness at T_{room} while
621 higher values of E'_{Tdef} , thus resulting in an overall stiffness reduction of about 70% ($E'_{\text{Troom}} = 1110$
622 MPa vs $E'_{\text{Troom}} = 1010$ MPa and $E'_{\text{Tdef}} = 340$ vs $E'_{\text{Tdef}} = 280$ MPa for extruded vs printed items).
623 Samples having different original shapes, fabricated *via* both techniques, showed the ability to
624 undergo shape recovery induced by water at room temperature and $37\text{ }^\circ\text{C}$, regardless of the presence
625 of CFF (Table 6 and 7). With originally I-shaped samples, recovery turned out faster with respect to
626 the previously tested ones, which was consistent with the T_g values relevant to the PVA05GLY-CFF
627 formulation. In spite of a comparable extent of recovery, t_{RIfinal} was nearly doubled for the extruded
628 specimen as compared with the printed one. This was in agreement with the findings obtained from
629 tracer-free specimens and is not surprising on account of the layered nature of items attained by
630 additive manufacturing.

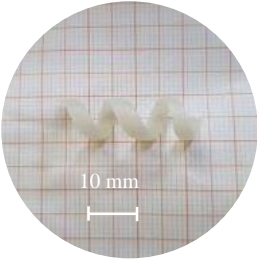


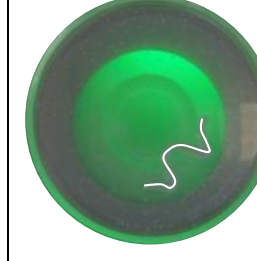

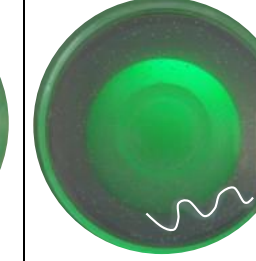
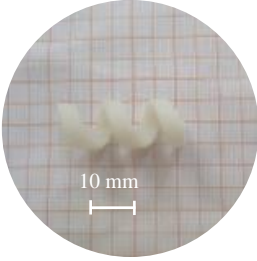



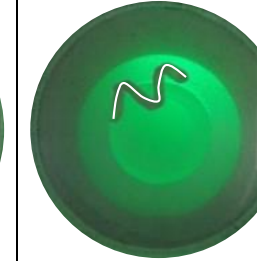
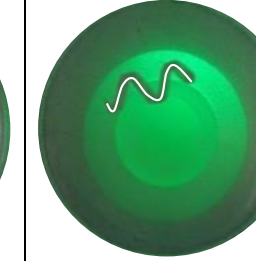
631

632 **Table 6:** RI_{final} values and corresponding t_{RIfinal} from specimens having original I- and helix-shape
633 tested at room temperature

	Original shape	RI_{final}	t_{RIfinal} (min)
HME	I-shape	0.94	40
	helix-shape	0.75	26
FDM	I-shape	0.76 ^a	12 ^a
	helix-shape	0.71	12

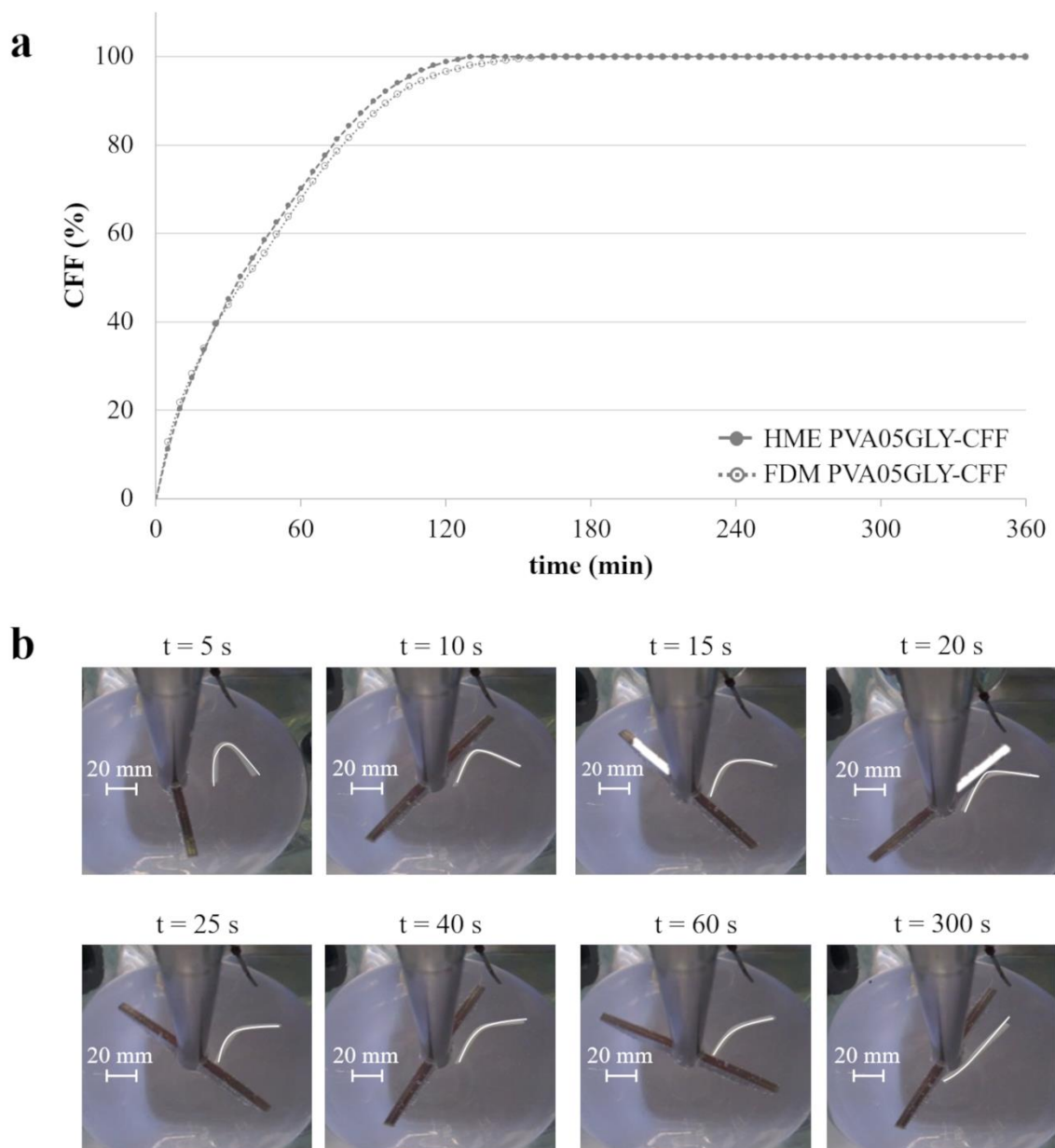
634 ^a determination hindered by dissolving of the polymer with possible distortion
635 of the specimen

636 **Table 7:** photographs acquired during shape recovery experiments (37 °C) of PVA05GLY-CFF specimens having original helix shape, obtained by
 637 HME and FDM, programmed to take on a temporary I-shape. A solid line is superimposed to highlight the recovery process

HME						
FDM	 original shape	 1 min	 5 min	 10 min	 15 min	 30 min

638

639 Release of the tracer from extruded and printed samples having original I-shape was studied after
 640 programming and fixing of the temporary U-shape, in order to evaluate the performance during
 641 recovery (Figure 8a). For this purpose, photographs of specimens were collected throughout the
 642 release test, and selected images relevant to printed items are reported in Figure 8b by way of
 643 example.
 644



645
 646 **Figure 8:** a) release profiles from originally I-shaped PVA05GLY-CFF specimens obtained by
 647 HME and FDM following programming and fixing of the temporary U-shape and b) photographs of
 648 the printed specimen at successive time points during the test. A solid line is superimposed to
 649 highlight the recovery process.

650 Release curves from extruded and printed specimens were almost superimposed. The release started
651 without any lag phase and was completed within 2 h. Notably, with both extruded and printed
652 specimens, the original straight shape was almost fully recovered before $t_{10\%}$, the most marked
653 changes occurring within 60 s.

654

655 **Conclusions**

656 Indwelling drug delivery systems could be highly beneficial in the treatment of bladder diseases by
657 increasing the intravesical residence time of drugs and compensating for the relevant washout. Such
658 systems would thereby overcome failures and discomfort connected with repeated instillations
659 through catheters. Moreover, they would allow different release kinetics to be established. The use of
660 SMPs, in view of their ability to take on a programmed/temporary shape and recover the
661 permanent/original one in the presence of an external *stimulus*, was regarded as an innovative strategy
662 to develop retentive drug delivery systems with convenient administration mode. Among
663 swellable/erodible SMPs characterized by water-induced shape memory response and good melt-
664 processability, PVA of pharmaceutical-grade was selected for design and fabrication *via* hot-
665 processing techniques, namely FDM 3D printing and HME, of an indwelling device for intravesical
666 drug administration involving no removal procedure. In this respect, application of a 3D printing
667 technique to an SMP would notably provide the basis for 4D printing because of the programmed
668 changes in shape of the printed item occurring over time.

669 Starting from formulations based on PVA of different molecular weights, specimens having diverse
670 original shapes and compositions were successfully extruded and printed. After programming and
671 fixing of a temporary shape, these exhibited the desired ability to recover the original one following
672 interaction with aqueous fluids, and the overall recovery as well as its rate were consistent with those
673 expected according to the thermo-mechanical properties of the investigated materials. The recovery
674 process was relatively fast, particularly at 37 °C, which was considered potentially advantageous in
675 the prospect of achieving prompt retention of the final system immediately after insertion into the

676 bladder. The softening upon glass-rubber transition of the polymer would impart favorable hardness
677 characteristics to the device, such that limited mechanical impact on the bladder epithelium could be
678 ensured. Purposely fabricated samples containing an analytical tracer turned out able to modify the
679 release of the latter before complete dissolution, yielding prolonged release patterns consistent with
680 the molecular weight of PVA employed. Thus, multi-functionality of the PVA-based materials
681 investigated was highlighted, entailing water-induced shape shifting, controlled release of a tracer
682 and erosion/dissolution in biological fluids. More extended and varied release profiles, associated
683 with diversified retention times, could be pursued by appropriate formulation and processing choices,
684 such as selection and combination of polymers having higher molecular weights, modulation of the
685 amount of plasticizer, addition of release modifiers and improvement of the equipment to ease
686 processing.

687 Although preliminary in scope, this study pointed out the viability of the proposed approach based
688 on hot-processing of a pharmaceutical-grade polymer having water-induced shape memory response
689 in the manufacturing of retentive intravesical delivery systems, opening up new perspectives in
690 application of 4D printing to the pharmaceutical field.

691

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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.

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