

Vat Photopolymerization 3D Printing of Hydrogels Embedding Metal–Organic Frameworks for Photodynamic Antimicrobial Therapy

Original

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(Article begins on next page)

24 photoinitiator, enabling the precise printing of complex structures. In addition, these
25 crystals impart photothermal and photodynamic capabilities to the printed object. The
26 antibacterial assay confirms the potent photothermal/photodynamic bactericidal
27 properties of the printed GelMA/MOF hydrogels. The hydrogel with the highest MOF
28 content exhibited over 99.99% antibacterial efficiency against both *Gram-positive*
29 *Staphylococcus aureus* and *Gramnegative Escherichia coli* after 30 min of light
30 exposure ($\sim 30 \text{ mW/cm}^2$, $\lambda \geq 420 \text{ nm}$). Simultaneously, hemolysis and cytotoxicity
31 evaluations validated their excellent biocompatibility. The findings presented here
32 introduce a strategy for integrating photosensitive MOF and 3D printing to fabricate
33 size-adjustable photothermal/photodynamic monoliths and patches, opening
34 perspectives towards personalized treatment for wound management.

35 **Keywords:** GelMA, porphyrinic MOF, vat photopolymerization 3D printing,
36 photothermal, photodynamic

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46 **1. Introduction**

47 Over the years, wound infection has posed a major threat to human health due to
48 the heightened vulnerability of injured skin to bacterial invasion and proliferation ¹.
49 To address this issue, a substantial number of antibiotics have been developed and
50 implemented for practical applications ². However, conventional antibiotics are
51 becoming less effective due to the emergence of antibiotic-resistant strains resulting
52 from their common misuse and overuse ³. Therefore, alternative approaches that can
53 effectively face bacterial infections are urgently needed. Recently, photodynamic
54 therapy (PDT) has emerged as a promising strategy, which can inactivate pathogens
55 by generating reactive oxygen species (ROS) through photochemical reactions.
56 Importantly, ROS sterilize the bacteria by disrupting the cell membrane structure,
57 thereby mitigating the concern of bacterial resistance ^{4,5}.

58 Currently, an increasing number of materials have been demonstrated to produce
59 ROS for achieving PDT, such as carbon quantum dots (CQDs), molybdenum disulfide
60 (MoS₂), and metal-organic framework (MOF) ⁶⁻⁸. Among them, MOF coordinated by
61 organic linkers and metal nodes is an emerging class of photodynamic materials with
62 ultrahigh porosity ⁹. In particular, porphyrinic MOF possesses not only exceptional
63 photodynamic effects but also excellent photothermal performance, making them
64 have great potential in clinical therapeutics ¹⁰. Numerous studies on porphyrinic MOF
65 for chronic wounds, ophthalmic, and even oral treatments have been reported recently
66 ¹¹⁻¹³. However, such nano-sized solids are not suitable for direct use in the human
67 body due to the leakage and residual hazards, and apparently some reports on medical

68 MOF have ignored this crucial consideration. Fortunately, encapsulating and
69 immobilizing MOF within hydrogel systems seems to be a feasible strategy. For
70 instance, Gwon et al. employed diacrylated polyethylene glycol and 4-arm-thiolated
71 PEG as the photocuring matrix to fabricate bioactive MOF-embedded hydrogels.
72 These hydrogels can kill bacteria by the slow release of metal ions through the
73 degradation of embedded MOF ¹⁴. Huang et al. also reported a multifunctional
74 composite hydrogel, which encapsulated modified curcumin-based MOF for chronic
75 wound management ¹⁵. Although these studies have highlighted the great potential of
76 MOF-based hydrogels in wound dressings, building complex shapes and conformable
77 patches to closely match the skin defects is also of significant importance for clinical
78 needs ¹⁶. Specifically, each patient's wound is distinct, differing in size, depth,
79 location, and severity ¹⁷. Tailoring the dressing to the specific characteristics of the
80 wound could ensure optimal coverage and contact with the affected area, promoting
81 effective healing ¹⁸. Therefore, here we propose to employ Digital Light Processing
82 (DLP) 3D printing technology to fabricate MOF-loaded hydrogels, aiming to satisfy
83 the personalized antimicrobial treatment of different-shape wounds.

84 DLP is a precise and efficient additive manufacturing (AM) technique that
85 employs a projector-based system to selectively cure photosensitive resins layer by
86 layer, enabling to create complex three-dimensional (3D) objects ^{19, 20}. Notably,
87 compared to other 3D printing techniques, DLP offers unique advantages such as
88 higher printing resolution and accuracy, faster speed, and smoother surface finish ^{21, 22}.
89 In healthcare, DLP 3D printing enables the rapid production of wound dressings

90 customized to specific shapes, which is especially crucial during emergencies when
91 there is a sudden surge in patient demands. Furthermore, it may be compatible with
92 the embedding of electronic components during the manufacturing process,
93 facilitating the development of smart medical devices or dressings with real-time
94 monitoring, diagnostic, and even therapeutic functions^{23,24}. However, there has been
95 limited research on DLP printed hydrogel dressings for wound therapy. Up to now,
96 many reports have increasingly indicated that DLP is an outstanding strategy for
97 fabricating hydrogels with complex 3D shapes employing both synthetic and natural
98 raw materials²⁵⁻³⁰. Among different categories of bio-based hydrogel photocurable
99 materials, gelatin methacrylate (GelMA) has been widely used in tissue engineering,
100 wound repair, and drug release system because of its excellent biocompatibility and
101 photopolymerizable characteristics³¹⁻³³. The high optical transparency of GelMA
102 hydrogels can provide good light transmission for the embedded photosensitizers to
103 initiate photochemical reactions, as demonstrated by several publications³⁴⁻³⁷.

104 In this study, a porphyrinic MOF (PCN-224) composed of Zr-oxo clusters and
105 5,10,15,20-tetrakis (4-carboxyphenyl) porphyrin (H₂TCPP) ligands was chosen as the
106 filler for the DLP 3D printing³⁸. PCN-224 has been widely utilized as a PDT agent
107 due to its advantages of efficient diffusion of ROS, great chemical/physical stability,
108 and high biocompatibility³⁸⁻⁴⁰. To the best of our knowledge, it's the first time that
109 porphyrinic MOF are employed as functional fillers in this advanced technology.
110 Briefly, different concentrations of this MOF were incorporated into GelMA matrix to
111 fabricate GelMA/MOF hydrogels using a DLP 3D printer. Taking into account the

112 light-absorption of the MOF, those can be used as smart dyes, able to improve
113 printing precision and impart functional properties to the objects ⁴¹. Consequently, the
114 curing behavior of the GelMA/MOF formulations was measured by photorheology
115 and printing parameters were optimized to fabricate complex shape structures. The
116 printed GelMA/MOF hydrogels were systematically characterized by morphological
117 observation, water retention, swelling and mechanical properties. The photothermal
118 and photodynamic characterizations of GelMA/MOF hydrogels were also performed.
119 In addition, the antibacterial efficiency of the GelMA/MOF hydrogels against Gram-
120 positive *Staphylococcus aureus* (*S. aureus*) and Gram-negative *Escherichia coli* (*E.*
121 *coli*) was evaluated under visible light (~ 30 mW/cm², $\lambda \geq 420$ nm). The hemolysis and
122 cytotoxicity assays were conducted to assess the hemocompatibility and
123 cytocompatibility, respectively. All these findings indicated that this strategy enables
124 the customization of dressings to match the specific contours of the wound, ensuring
125 optimal contact with the wound surface and thereby achieving effective
126 photothermal/photodynamic therapy.

127

128 **2. Experimental**

129 **2.1 Materials**

130 The gelatine (Gel) used as precursor of gelatine methacrylate (GelMA) is Type B
131 gelatin from bovine skin, Bloom 50-120 bought from Merck, Italy. Four types of
132 GelMA type B (DS: 60%, 80%, 90%, 95%) were lab-synthesized following the
133 procedures previously reported ^{33, 42-45}. ZrOCl₂·8H₂O (99.9%), 5,10,15,20-Tetrakis(4-

134 carboxyphenyl)porphyrin (TCPP, 97%), benzoic acid (99.5%) and 1,3-
135 Diphenylisobenzofuran (DPBF) were purchased from Macklin Biochemical
136 Technology, China. Water-soluble diphenyl (2,4,6-trimethylbenzoyl)phosphine oxide
137 (TPO-SDS) and other chemicals were obtained from Merck, Italy. All chemicals were
138 used as obtained without further purification.

139 **2.2 Synthesis of MOF (PCN-224) nanoparticles**

140 PCN-224 nanoparticles were synthesized according to previous method ³⁸. In
141 brief, 1.5 g of benzoic acid and 0.15 g of $ZrOCl_2 \cdot 8H_2O$ were dissolved in 10 mL
142 DMF under ultrasonication, then 0.05 g of TCPP was added in the DMF with
143 continuous ultrasonication. After that, the mixture was transferred in a Pyrex vial and
144 heated at 120 °C for 24 h. After the reaction, the mixture was naturally cooled to room
145 temperature and centrifuged (8000 rpm/min, 30 min) to obtain the precipitated
146 product. Subsequently, the product was washed with DMF twice and ethanol three
147 times to remove impurities. Finally, PCN-224 nanoparticles were collected after
148 drying in a vacuum oven at 60 °C for 12 h.

149 **2.3 Formulations**

150 GelMA/MOF formulations containing different concentrations (0.125, 0.25, 0.5,
151 1 mg/mL) of MOF nanoparticles were prepared, the notation used was GelMA/MOF_x
152 where x represents the concentration of MOF in the formulation. In detail, TPO-SDS
153 (5% to GelMA, w/w) and GelMA were dissolved in deionized water (DI water) under
154 ultrasonication to obtain GelMA precursor solution (30%, w/v). Then, MOF
155 nanoparticles were ultrasonically dispersed in DI water at different concentrations

156 (0.25, 0.5, 1, 2 mg/mL). Afterward, equal volumes of the GelMA precursor solution
157 and each MOF dispersion were mixed and vigorously stirred to obtain pre-printed
158 GelMA/MOF formulations. The GelMA precursor solution was mixed with an equal
159 volume of DI water to prepare pre-printed GelMA formulations, the final tested
160 concentrations were: 10%, 12.5%, 15% and 20% w/v.

161 **2.4 3D printing process**

162 The printing process of the formulations was carried out with the DLP 3D printer
163 (Asiga UV MAX27, Asiga, AUS) to fabricate GelMA and GelMA/MOFs hydrogels.
164 Before the printing, various shapes of models were created using Cinema 4D software
165 and converted in STL format.

166 Preliminary tests were carried out to assess light intensity and layer thickness.
167 The formulations were dropped on a vat and exposed for different times under LED
168 light with 40 mW/cm² intensity. Then, the formulations were exposed for a fixed time
169 to different light intensities to investigate the relationship between light intensity and
170 layer thickness.

171 The light intensity and the exposure time of each formulation was selected based
172 on these results; briefly, the slice thickness was settled as 0.2 mm. After the printing
173 process, each sample was carefully washed by 50 °C DI water to remove uncured
174 formulations and then post-cured for 2 min in a UV chamber. For sterilization, the
175 post-cured hydrogels were immersed in 70% ethanol for 1 h and kept in sterile
176 phosphate buffered solution (PBS) at 4 °C.

177 **2.5 Characterization**

178 The morphology of synthesized MOF was observed by a transmission electron
179 microscope (TEM, JEM-2100, Japan), and the average diameters and size
180 distributions of MOF were measured by using Nano Measurer (China). The crystal
181 structure of MOF was characterized by X-ray diffractometer (XRD, D2 PHASER,
182 Germany), and the scanning angle was ranged from 2° to 40° with a step size of
183 2°/min. NEXUS 470 spectrometer (USA) was employed to record the Fourier
184 transform infrared spectroscopy (FTIR). Photorheological measurements were
185 performed using a rheometer (Physica MCR 302, Austria) with a broad band UV-light
186 source (Hamamatsu LC8 lamp, Japan) at light intensity of 45 mW/cm². The
187 morphologies of printed GelMA and GelMA/MOF hydrogels were characterized by a
188 field emission scanning electron microscope (FESEM, Regulus8100, Japan). The UV-
189 vis spectra were measured by a BioTek Synergy HTX Multimode Reader (USA). The
190 mechanical property of printed hydrogels was tested by using dynamic mechanical
191 analysis (DMA, METTLER TOLEDO DMA 1, Switzerland). All cylindrical
192 hydrogels ($\Phi = 10$ mm, $H = 6$ mm) were carried out in compression mode
193 (Displacement = 0.05 mm, Frequency = 10 Hz) at 25 °C and 37 °C. The ASIGA 3D-
194 printer (Max-UV27, Alexandria, AUS) was employed for DLP 3D printing process,
195 the printer employs a light source of 385 nm and has a nominal X-Y resolution of $27 \times$
196 $27 \mu\text{m}^2$. A 3D optical scanner (E3, 3Shape, Denmark) was utilized to evaluate print
197 resolution.

198 **2.6 Swelling and water retention tests**

199 The swelling behavior and water retention of the printed hydrogels were

200 measured according to pervious methods with slight modifications ^{46, 47}. For the
201 swelling behaviors, the printed cube sample ($4 \times 4 \times 4 \text{ mm}^3$) was freeze-dried to
202 obtain a dry weight (W_0). Then, the lyophilized samples were transferred to PBS
203 solution and incubated in $37 \text{ }^\circ\text{C}$ water for 48 h. At every interval, the sample was
204 carefully wiped with filter paper and weight as (W_t). The swelling rate was calculated
205 according to Eq. (1):

$$206 \quad \textit{Swelling ratio} (\%) = \frac{W_t - W_0}{W_0} \times 100 \quad (1)$$

207 Regarding the water retention test, a cube sample ($4 \times 4 \times 4 \text{ mm}^3$) was immersed
208 in PBS for 24 h, then the sample was carefully wiped with filter paper to remove the
209 excess moisture and weight as (W'_0). The sample was placed at room temperature
210 (humidity: around 40%) and weighed it at different intervals (W'_t). The water
211 retention was calculated according to Eq. (2):

$$212 \quad \textit{Water retention} (\%) = \frac{W'_t}{W'_0} \times 100 \quad (2)$$

213 **2.7 Degradation test**

214 The degradation test was conducted according to a reported method ⁴⁸. In brief,
215 the freeze-dried hydrogels were added into pre-weighted plastic bottles (W_b) and
216 subsequently re-weighted (W_0). Then, 4 mL of PBS were added into each bottle and
217 the specimens were incubated at $37 \text{ }^\circ\text{C}$. At intervals of 1, 4, 8, 15, and 30 days, the
218 liquid in the corresponding bottles was removed and the bottles were dried in a
219 vacuum oven. The dried bottles were weighed (W_t) and the degradation percentage (D)
220 was calculated using the Eq. (3):

221
$$D (\%) = \frac{W_t - W_b}{W_0 - W_b} \times 100 \quad (3)$$

222 **2.8 Singlet oxygen (¹O₂) generation detected by DPBF**

223 DPBF was used as a specific probe to detect the ¹O₂ generation. Briefly, 4 mL of
224 50% ethanol containing DPBF (30 mg/L) was added to a plastic tube, then a printed
225 cylindrical sample ($\Phi = 10$ mm, $H = 1$ mm) was added in the bottom of this tube and
226 keep in the dark for 1 h. After that, this tube was exposed to an illumination (520 nm
227 laser) for 5 min. 200 μ L of the solution in this tube was pipetted in a 96 well-plate and
228 the UV-vis spectrum was recorded with a microplate reader every 1 min; in addition,
229 the solution after each measurement was pipetted back into the tube for the next
230 exposure.

231 **2.9 Antibacterial efficiency and SEM images of bacterial morphology**

232 The biocidal efficacy of printed GelMA and GelMA/MOF hydrogels against *S.*
233 *aureus* (ATCC 6538) and *E. coli* (ATCC 43895) were evaluated by a modified
234 AATCC 100-2004 Test ^{49, 50}. In detail, the sterile samples ($\Phi = 10$ mm, $H = 1$ mm)
235 were respectively placed on the bottom of a sterile 24-well plate, and 10 μ L of
236 bacterial suspension (10^6 colony-forming units/mL) was inoculated on each sample.
237 Then, a Xenon lamp (~ 30 mW/cm², $\lambda \geq 420$ nm) illuminated each sample for 30
238 minutes at a vertical height. Meanwhile, the same samples were tested in another 24-
239 well plate under darkness. Afterwards, 1 mL PBS was added to each well and
240 vortexed for 30 s to suspend bacteria, then the bacterial suspension was diluted
241 serially 3 times (10, 100, 1000-fold) and 50 μ L of the dilution was evenly dropped on
242 agar plates. After incubation at 37 °C for 16-24 h, the bacterial colonies on agar plates

243 were counted. All the biocidal experiments were carried out in triplicate.

244 **2.10 Hemolysis and Cytotoxicity assays**

245 The hemolysis assay was conducted according to a previous method⁵¹. In detail,
246 5 mL of anticoagulant whole blood was added to 10 mL of PBS solution and
247 centrifuged at 1500 rpm for 10 min to collect the underlying red blood cells (RBCs).
248 Then the obtained RBCs were injected in PBS to prepare 5% (v/v) RBCs/PBS
249 dilution. Afterwards, 0.5 mL of RBCs/PBS dilution was mixed with 1 mL of DI water
250 or PBS and incubated for 3 h to establish the positive or negative group. Meanwhile,
251 0.5 mL of RBCs/PBS dilution was added to 1 mL of PBS containing 10 mg of freeze-
252 dried GelMA or GelMA/MOF hydrogels, and co-incubated for 3 h to establish the
253 experiment groups. These mixtures were centrifuged at 2000 rpm for 10 min after the
254 incubation, and the absorbance of each supernatant was recorded by using a UV-vis
255 spectrophotometer. The hemolysis ratio was calculated by Eq. (4):

$$256 \quad \text{Hemolysis ratio (\%)} = \frac{A_{\text{hydrogel}} - A_{\text{negative}}}{A_{\text{positive}} - A_{\text{negative}}} \times 100 \quad (4)$$

257 where A_{positive} , A_{negative} , and A_{hydrogel} represent the absorbance of positive, negative,
258 and freeze-dried hydrogel groups at 540 nm, respectively.

259 The *in vitro* cytotoxicity of printed GelMA and GelMA/MOF hydrogels was
260 performed by CCK-8 assay method using mouse fibroblast cells (L929)⁵². Briefly, the
261 L929 cells were revived in Dulbecco's Modified Eagle Medium (DMEM) under a 5%
262 CO₂ atmosphere at 37°C, subsequently seeded in a 96-well plate and cultured for 24 h.
263 Meanwhile, 10 mg of sterile hydrogel samples were incubated in DMEM at 37°C for
264 24 h to obtain the sample extracts. Afterward, the culture medium in the 96-well plate

265 was aspirated and replaced with an equivalent volume of sample extracts. In addition,
266 the 0.1% Triton X-100 was used as the positive control and DMEM as the negative
267 control. The plate was then incubated for an additional 48 hours. The absorbance of
268 the cell culture medium was measured at 450 nm after the addition of CCK-8 reagent.
269 The cell viability of hydrogel samples was calculated by Eq. (5):

$$270 \quad \text{Cell viability (\%)} = \frac{OD_{\text{sample}} - OD_{\text{positive}}}{OD_{\text{negative}} - OD_{\text{positive}}} \times 100 \quad (5)$$

271 where OD_{positive} , OD_{negative} , and OD_{sample} represent the absorbance of positive
272 control, negative control, and hydrogel sample groups, respectively.

273 **2.11 Statistical analysis**

274 The statistical analysis employed ANOVA and Student's t-test. All experimental
275 data were presented as mean \pm standard deviation, with statistical significance
276 determined at $P < 0.05$. The standard deviations in all figures were represented by
277 error bars.

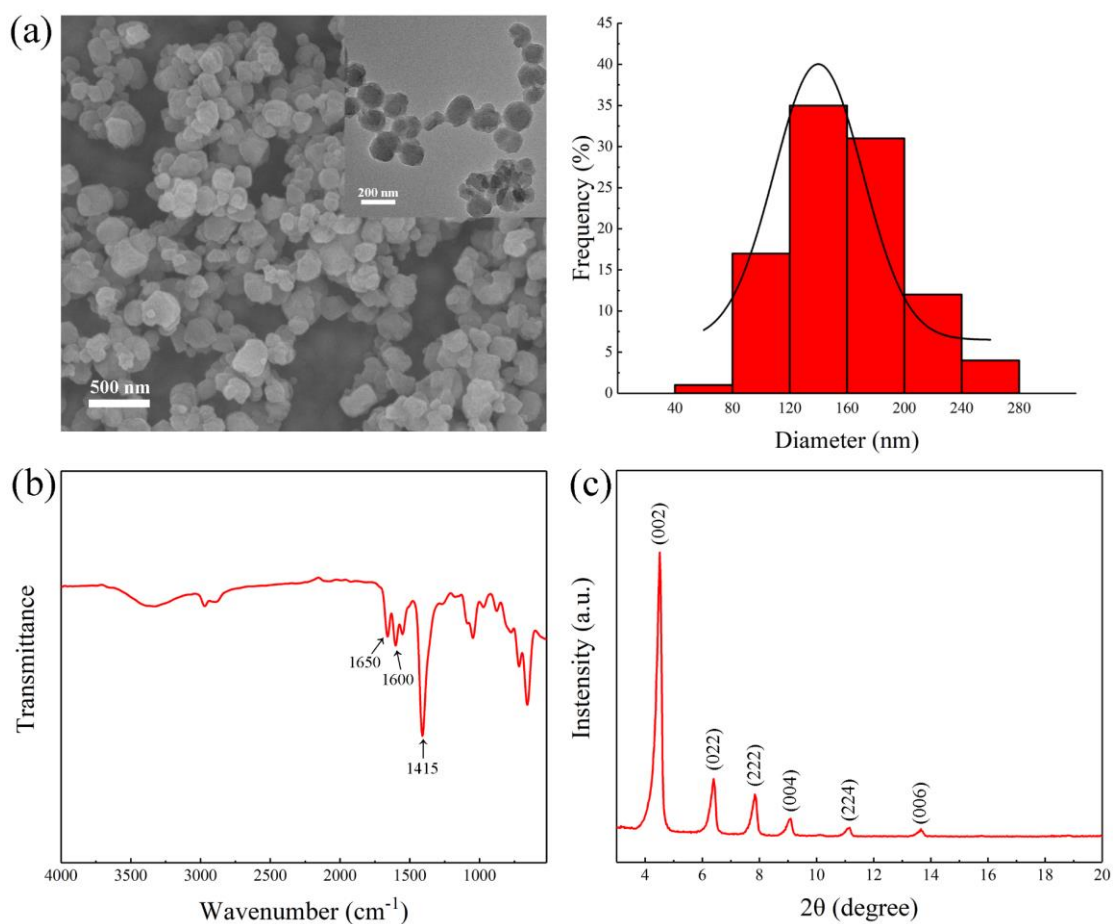
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279 **3. Results and discussions**

280 **3.1. Synthesis and characterization of MOF**

281 The FESEM and TEM images in Fig. 1a illustrate the synthesis of MOF particles,
282 which exhibit a predominantly spherical crystal morphology with an average diameter
283 of approximately 158 nm and a size range spanning from 77 to 257 nm. The chemical
284 and physical structures of the synthesized MOF were characterized by FTIR and XRD,
285 respectively. As shown in FTIR spectrum (Fig. 1b), the peak around 1650 cm^{-1} , 1600
286 cm^{-1} , and 1415 cm^{-1} were ascribed to C=O stretching vibration, C=C stretching

287 vibration and C-N bending vibration, respectively ³. The XRD pattern exhibited
288 several strong peaks around 4.6°, 6.4°, 7.9°, 9.1°, 11.2° and 13.7°, corresponding to
289 the (002), (022), (222), (004), (224), and (006) crystal facets of PCN-224, respectively
290 ⁵³. The results of FTIR and XRD characterizations are consistent with previous
291 reports, confirming the successful synthesis of MOF (PCN-224) nanoparticles ⁵⁰.



292

293 Fig. 1. (a) Morphology images and diameter distribution of the synthesized MOF. (b)

294

FTIR spectrum of MOF. (c) XRD patterns of MOF.

295

296 3.2. Formulation design

297

In preliminary experiments, GelMAs with different degrees of methacrylation

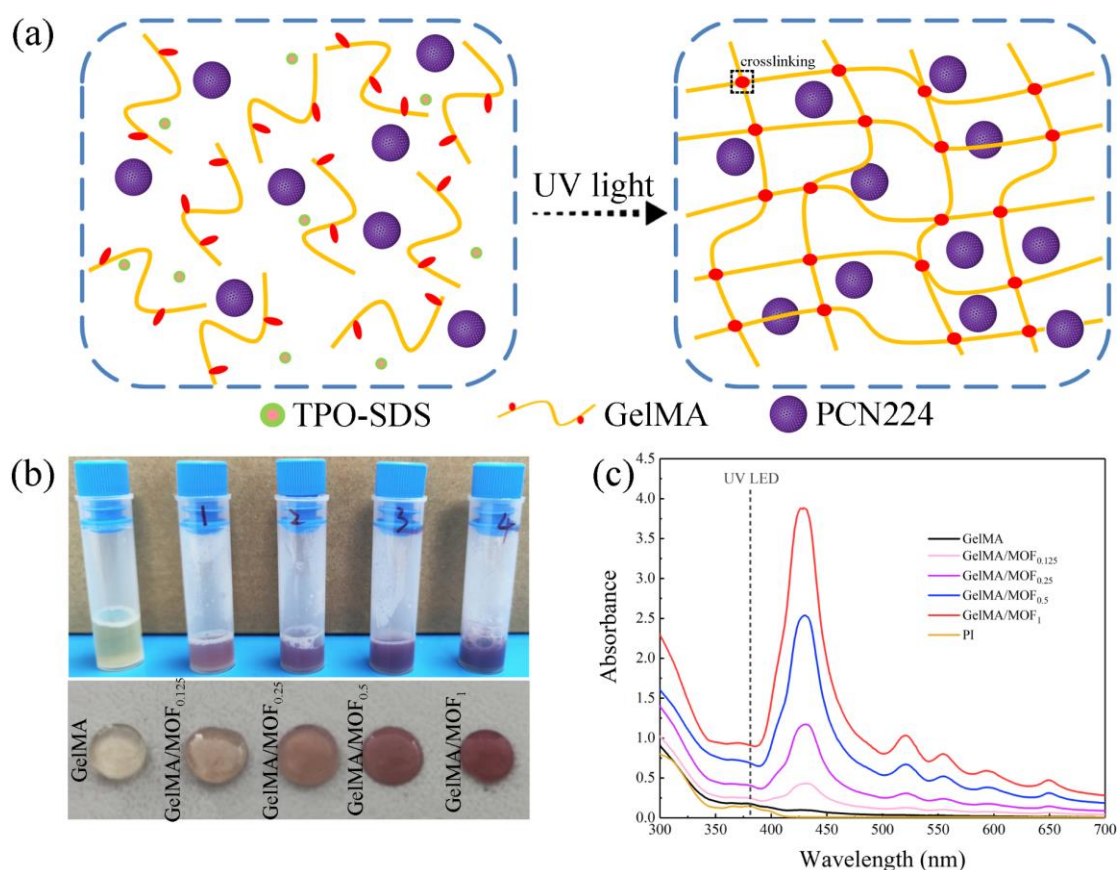
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(60%, 80%, 90%, and 95%) were used to print cubic hydrogels. Each type of GelMA

299 was printed at different concentrations of 10%, 12.5%, 15%, and 20% w/v in PBS or
300 DI water. As shown in Fig. S1 in Supporting Information file, the GelMA
301 formulations at low concentrations (10% and 12.5%) exhibited problematic cubes'
302 printing, while the high concentration (20%) adversely affected the transparency. In
303 contrast, the GelMA hydrogels with a concentration of 15% displayed better
304 printability and transparency. Especially GelMA with a methacrylate substitution
305 degree of 90% (GelMA₉₀) showed the best printing result. Therefore, GelMA₉₀ at a
306 concentration of 15% was used as the polymer matrix for the preparation of
307 GelMA/MOF formulations.

308 The schematic illustration of GelMA/MOF hydrogel formation mechanism is
309 depicted in Fig. 2a. After exposure to UV light, the GelMA molecules are covalently
310 crosslinked, forming a dense and stable gel network that encapsulates MOF
311 nanoparticles. Fig. 2b exhibits the GelMA and GelMA/MOF formulations and the
312 corresponding hydrogels. Obviously, GelMA formulation can form a highly
313 transparent hydrogel after photopolymerization. After adding MOF, the color of
314 various GelMA/MOF formulations and their corresponding hydrogels turned to
315 darker with increasing MOF concentration. The UV-vis absorbance spectra of GelMA,
316 GelMA/MOF formulations and photoinitiator (PI) solution (0.75%, w/v) were
317 measured. As exhibited in Fig. 2b, the introduction of MOF leads to enhanced light
318 absorption at 385 nm, meaning a competition for light absorption between MOF and
319 PI, which would affect the photopolymerization of GelMA during the printing process.
320 This competition could be useful for DLP to improve the printing precision and to

321 prevent undesired curing out of the exposed areas ⁴¹. To testify this, the GelMA and
 322 various GelMA/MOF formulations were printed using two STL models: one featuring
 323 a cube with vertical cylindrical holes and the other with horizontal cylindrical holes.
 324 As depicted in Fig. S2a, the GelMA ink encounters challenges in forming the desired
 325 hole inside the cube due to excessive photopolymerization. In contrast, Fig. S2b
 326 demonstrates that the internal hole structure appears to be more easily printed after
 327 incorporating the MOF. This phenomenon indicates that adding a moderate amount of
 328 MOF can enhance printing accuracy, enabling the creation of 3D objects with more
 329 complex structures.



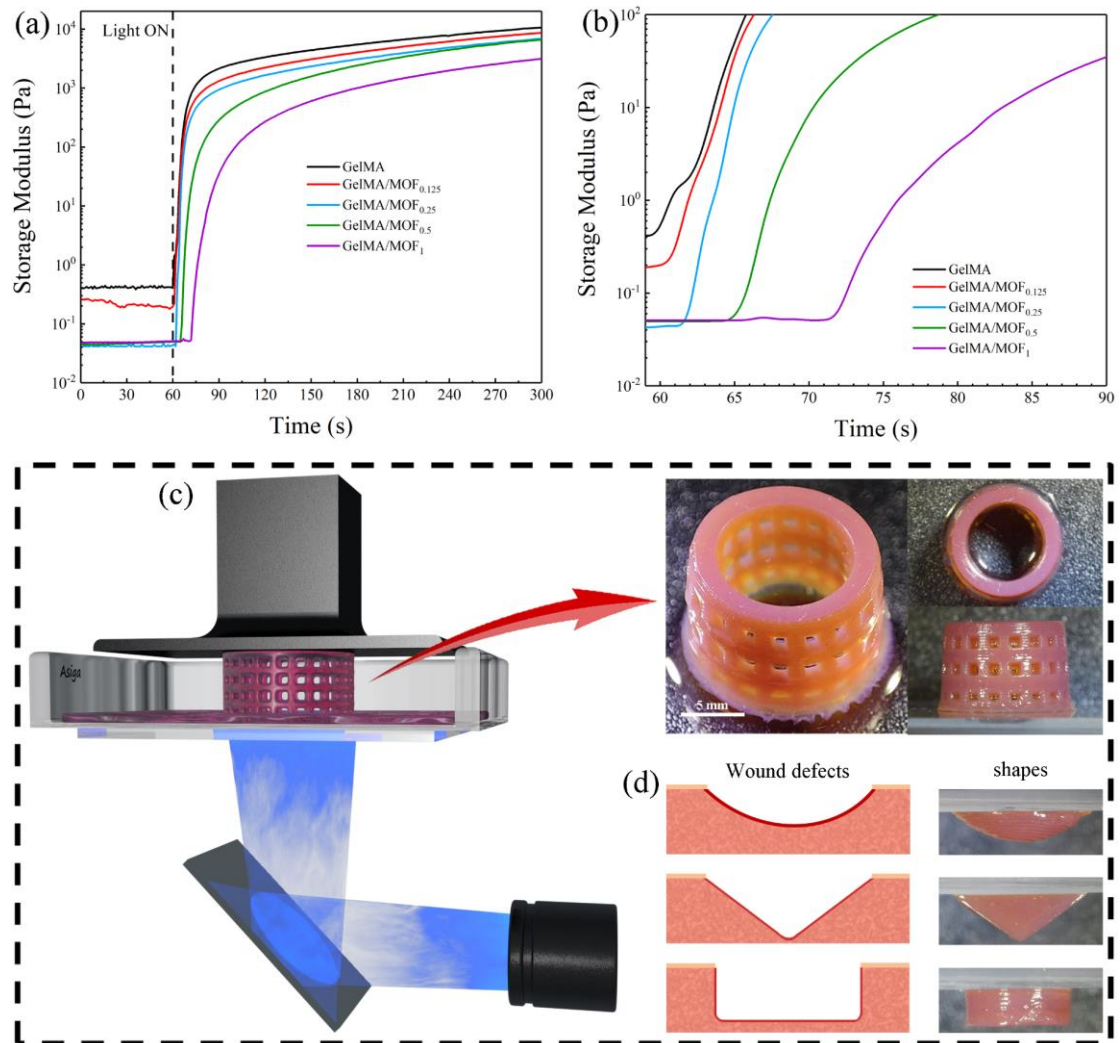
330
 331 Fig. 2. (a) Schematic illustration of the cross-linked network of GelMA/MOF
 332 hydrogel. (b) Photographs of various formulations and corresponding hydrogels. (c)
 333 UV-vis absorbance spectra of GelMA formulation, GelMA/MOF formulations and PI

334 solution (0.75%, w/v).

335 Considering the effect of different MOF concentrations on photopolymerization,
336 additional investigations were further conducted to determine the DLP printing
337 parameters, specifically photorheology and curing behavior tests. As shown in Fig. 3a,
338 all the formulations show rapid increase of G' modulus, indicating that gels are
339 formed in relatively short periods upon UV irradiation. This is a first indication of
340 their suitability for DLP 3D printing, in principle. However, the presence of MOF
341 induced variations in the photopolymerization kinetics of GelMA matrix. The start of
342 curing reaction of the GelMA/MOF formulations was gradually delayed as the MOF
343 concentrations increased (Fig. 3b), witnessed by an increased latency time (up to 13 s
344 for GelMA/MOF₁). Meanwhile, also, the final storage modulus of the cured hydrogels
345 decreases, indicating less cross-linked networks. These phenomena can be ascribed to
346 the competition of UV light between MOF and PI, which decreases the rate of
347 photoinitiation and thus the final conversion of acrylic double bonds⁴¹. To further
348 determine the parameters for printing process, the curing behavior of GelMA and
349 GelMA/MOF formulations were tested. As shown in Fig. S3a, these curves describe
350 the relationships between the light intensity and curing thickness of the formulations.
351 In addition, the relationships between the exposure time and the curing thickness are
352 also tested (Fig. S3b). As expected, the curing thickness and the exposure time are
353 linearly correlated at a constant light intensity⁵⁴. These results are important for
354 establishing optimal parameters in practical printing.

355 After optimizing the printing parameters, the fabrication of the GelMA/MOF

356 hydrogels was conducted. Fig. 3c illustrates the fabrication process using the DLP
357 printer. This equipment is based on the localized irradiation of pixels, following a
358 digital model file, which enables the fabrication of a single layer of one object. Then,
359 the solidified layer was moved upward, allowing the bottom of the vat to be covered
360 with a new layer of uncured resins, and consequently allowing to perform this process
361 over and over, until obtaining the desired 3D object ⁵⁵. In this case, once the curing
362 behavior was determined, the GelMA/MOF hydrogels with complex 3D structures
363 could be printed, obtaining objects with well-defined edges and holes, also in z
364 direction. It must be noted that such complexity is not trivial for formulations which
365 contain more than 80% of water, and the definition here obtained is in good
366 agreement with the results obtained in vat photopolymerization for formulations with
367 similar GelMA content ⁵⁶. Fig. S4 demonstrates the high model fidelity achieved by
368 DLP 3D printing, with errors of the object measured basically within 0.1 mm. In
369 addition, Fig. 3d exhibits the various shapes of GelMA/MOF hydrogels printed
370 according to different wound defects, implying the potential to flexibly manufacture
371 hydrogels matching the wound defect using DLP technology, thereby enabling
372 personalized wound management.



373

374 Fig. 3. (a) Photorheological curves of GelMA and GelMA/MOF formulations. (b)

375 Photopolymerization kinetics of GelMA and GelMA/MOF formulations within 30 s

376 of UV irradiation. (c) Schematic illustration of the printing process and the

377 corresponding product. (d) Various shapes of wound defect models and their

378 corresponding printed GelMA/MOF hydrogels.

379

380 3.3. Characterization of 3D-printed GelMA/MOF hydrogels

381 The micro-structure of the 3D-printed hydrogels were observed by FESEM after

382 freeze-drying. Fig. 4a and b show that the morphology of lyophilized 3D-printed

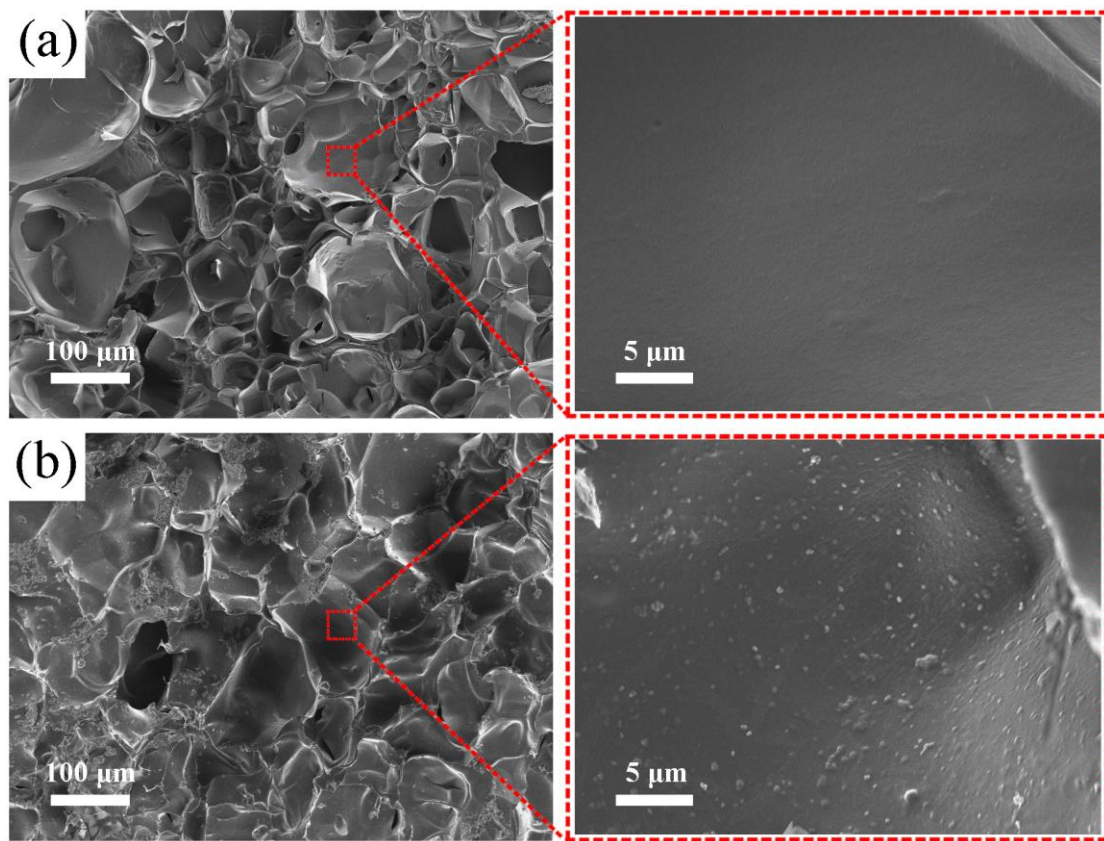
383 GelMA and GelMA/MOF₁ hydrogels contain highly anisotropic networks and typical
384 microporous structure, consistent with a cross-linked internal structure and suggesting
385 large liquid absorption capacity. In comparison of the magnified images of Fig. 4a
386 and b, the GelMA shows a relatively smooth surface, while GelMA/MOF₁ shows a
387 rougher surface, which can be attributed to the presence of the insoluble granular
388 MOF in GelMA matrix. The effect of the higher content of MOF are here showed, but
389 similarly the GelMA/MOF_{0.125}, GelMA/MOF_{0.25}, and GelMA/MOF_{0.5} specimens
390 display the cross-linked and microporous structure, as reported in Fig. S5 in
391 Supporting Information file. Therefore, it can be inferred that the MOF (as the filler)
392 plays a role during curing, but once optimized printing parameters exerts little
393 influence on the micro-structure of photopolymerized GelMA matrix, owing to the
394 precise control offered by DLP technology for photopolymerization.

395 The mechanical properties of the 3D-printed GelMA/MOF hydrogels were
396 assessed by DMA at 25 °C and 37 °C. As shown in Fig. 5a and b, the storage modulus
397 of GelMA-based hydrogel initially increases and then decreases with the increasing
398 concentration of MOF in the system. The probable cause of this phenomenon lies in
399 that at lower concentrations of MOF ($c \leq 0.25$ mg/mL), the carboxyl groups within
400 GelMA chains can coordinate with Zr₆ metal clusters present in MOF to form a more
401 densely packed hydrogel structure^{57, 58}. However, as the concentration of MOF
402 continues to increase, their presence affects the photopolymerization of the GelMA
403 matrix because of the optical competition, leading to a decrease in the crosslinking
404 density of the hydrogel, in good agreement with photorheology tests. In addition,

405 from Fig. 5a and b, as expected the increase in temperature enhances the chains
406 mobility, subsequently leading to a lower storage moduli ⁵⁹.

407 The swelling behavior and water retention of the printed hydrogels were also
408 investigated. The result of swelling ratios (Fig. 5c) indicates that all freeze-dried
409 hydrogels absorbed water rapidly, within 8 h, and then remained stable (measurement
410 up to 48 h), without being destroyed. Interestingly, the swelling ratio was slightly
411 reduced after adding a lower content of MOF ($c \leq 0.25$ mg/mL). This decrease could
412 be related to the higher crosslinking density of the nanofillers, which consequently
413 limits network expansion during absorption ³⁰. On the other hand, when the MOF
414 content is higher ($c \geq 0.5$ mg/mL), the swelling ratio increased, potentially attributed
415 to the looser network previously mentioned. To carefully tailor the final property of
416 the hydrogel, several factors must be considered. On the one hand, the presence of the
417 embedded nanofillers may hinder the movements of macromolecular chains
418 decreasing the free volume between the GelMA chains, and thus reducing swelling.
419 On the other hand, the effect of light absorption and printing parameters may result in
420 decrease of crosslinking density, modifying the swelling behavior of the composite
421 hydrogels ³⁰. Thus, according to desired applications, a proper trade-off must be
422 conducted regarding the printability, mechanical properties, and swellability of the
423 hydrogels. Fig. 5d exhibits the water retention capacity of printed hydrogels. All
424 hydrogels exhibited a similar pattern, losing moisture and reaching equilibrium within
425 8 h. In general, this is a drawback since hydrogels lose their flexibility drying. In view
426 of extending the applicability of hydrogels, in our next project, we aim at improving

427 the water retention performance of printed hydrogels. The degradation behavior of
428 printed hydrogels was also tested. As shown in Fig. S6, all hydrogels display good
429 degradability within 30 days. It is also evident that hydrogels with higher crosslinking
430 density (GelMA, GelMA/MOF_{0.125}, and GelMA/MOF_{0.25}) exhibited lower
431 degradability, whereas those with lower crosslinking density (GelMA/MOF_{0.5} and
432 GelMA/MOF₁) degraded more rapidly.



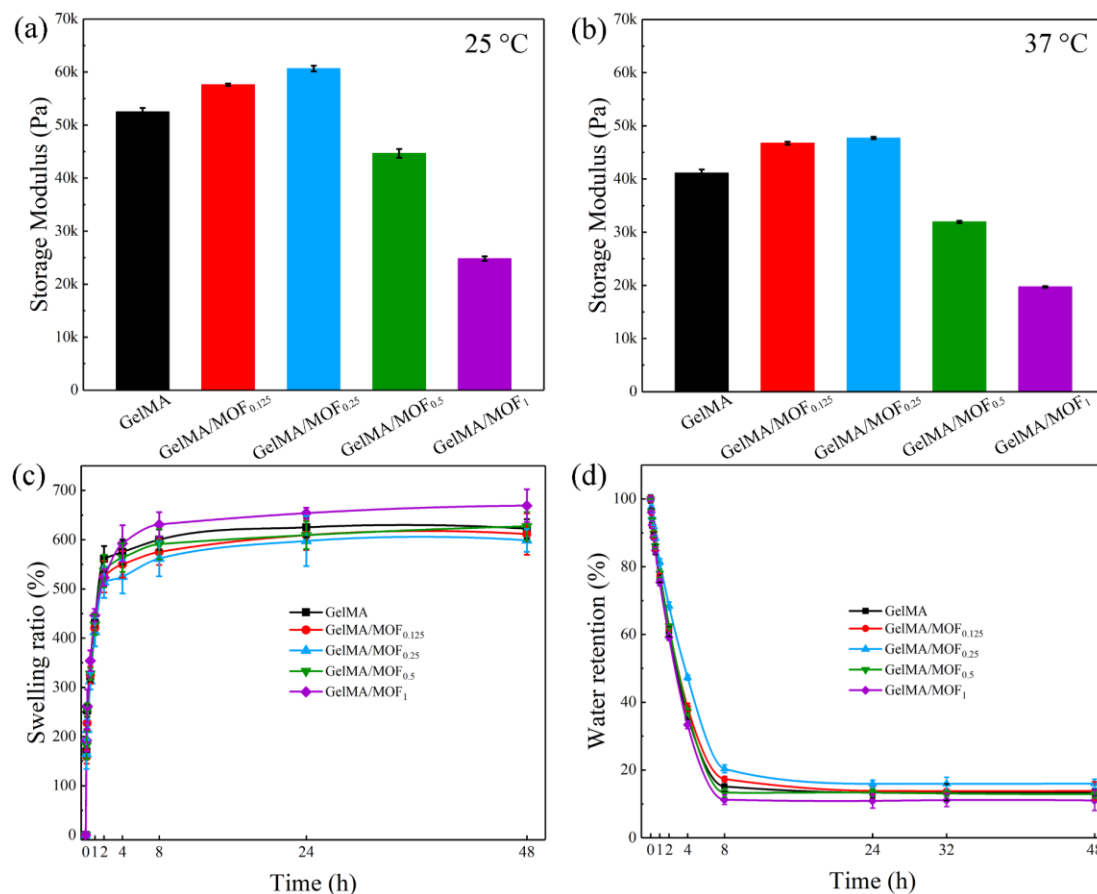
433

434 Fig. 4. Morphological structures of 3D-printed GelMA (a) and GelMA/MOF₁

435

hydrogels (b).

436



437

438 Fig. 5. (a-b) Storage modulus of 3D-printed GelMA and GelMA/MOF hydrogels at
 439 25 °C and 37 °C, respectively. (c) Swelling ratio. (d) Water retention.

440

441 3.4. Photothermal and photodynamic performances of printed GelMA/MOF hydrogels

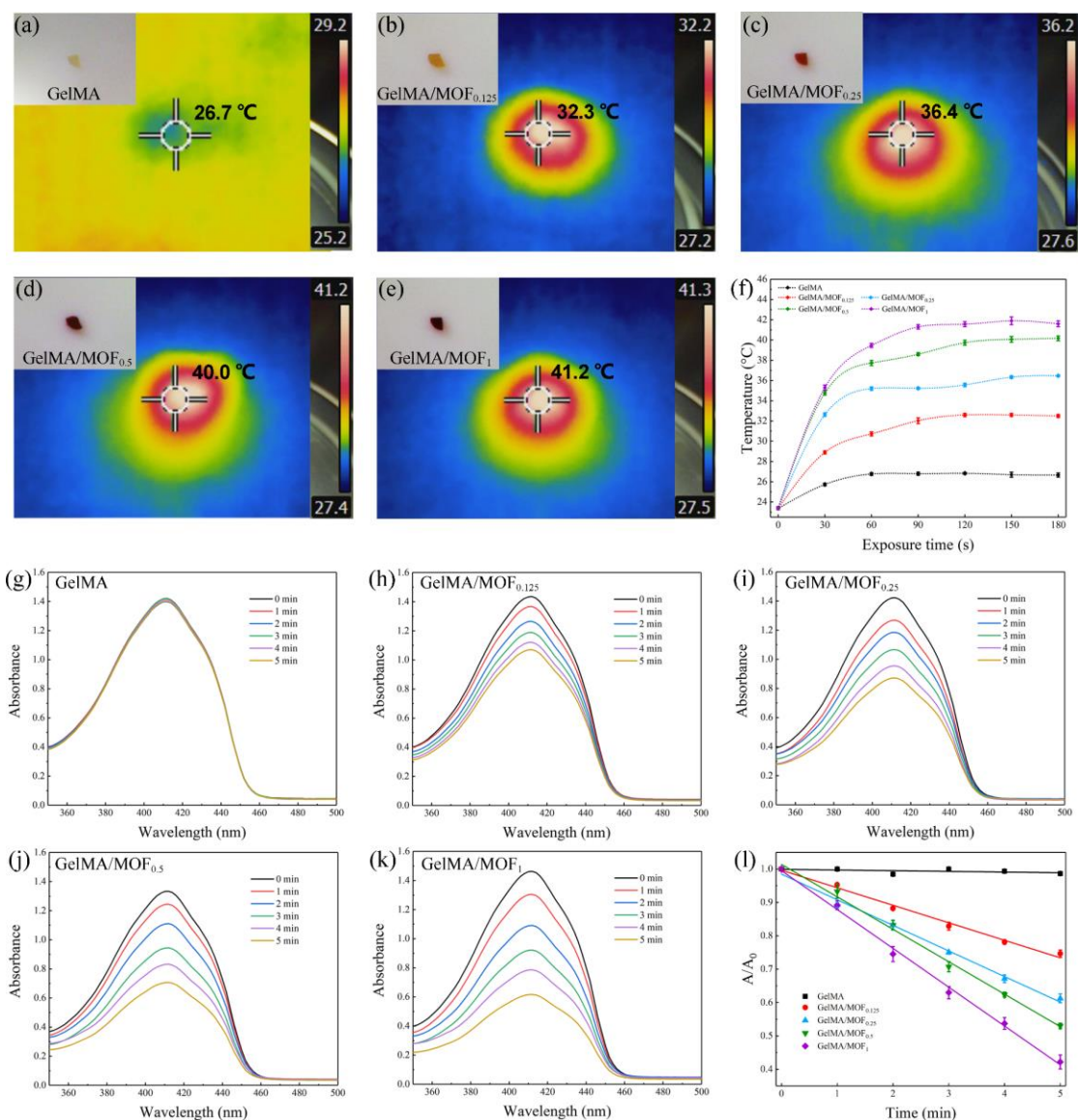
442 As a subclass of MOF materials, porphyrinic PCN-224 possesses excellent
 443 photothermal property and remarkable photodynamic activity^{38, 53, 60}. Hence, the
 444 photothermal and photodynamic performances of the 3D-printed GelMA/MOF
 445 hydrogels were investigated. As shown in Fig. 6a to e, after exposure to visible light
 446 for 180 s, the hydrogels reached a temperature of 26.7 °C for GelMA, 32.3 °C for
 447 GelMA/MOF_{0.125}, 36.4 for GelMA/MOF_{0.25}, 40.0 °C for GelMA/MOF_{0.5}, and 41.2 °C
 448 for GelMA/MOF₁, respectively. Fig. 6f also displays the photothermal curves of these

449 printed hydrogels within 180 s. Along with the increase in the amount of MOF
450 incorporated, the photothermal capacity gradually enhanced in the order
451 GelMA/MOF₁ > GelMA/MOF_{0.5} > GelMA/MOF_{0.25} > GelMA/MOF_{0.125} > GelMA.
452 Besides, it is worth noting that all the hydrogels exhibit a similar tendency, as the
453 exposure time to light increases, the temperature remains around its maximum value.
454 This phenomenon may be attributed to the evaporation of water within the hydrogel
455 system, which limits the increase in temperature.

456 PCN-224 has already been demonstrated able to produce ¹O₂ under light
457 irradiation, which could be specifically trapped by DPBF, leading to a decrease in the
458 absorbance at 415 nm ⁶¹. Hence, DPBF was selected as the ¹O₂ detector to compare
459 the photodynamic activity of printed GelMA/MOF hydrogels. Fig. 6g to k display the
460 UV-vis absorption spectra of DPBF co-incubated with these hydrogels after 5 min
461 irradiation. As predicted, the GelMA/MOF₁ hydrogel caused the most significant
462 decrease of absorption at 415 nm, indicating that this material could produce the
463 largest amount of ¹O₂, followed by GelMA/MOF_{0.5}, GelMA/MOF_{0.25},
464 GelMA/MOF_{0.125}, and GelMA. Similarly, the corresponding fitting curves (Fig. 6l)
465 depicting the absorption decrease over time (at 415 nm) further suggest that the
466 GelMA/MOF₁ achieved the highest efficiency in ¹O₂ yield, followed by
467 GelMA/MOF_{0.5}, GelMA/MOF_{0.25}, GelMA/MOF_{0.125}, and GelMA. Apparently, in this
468 case, the GelMA hydrogel (without MOF) showed no reduction in DPBF absorbance
469 under light irradiation for 5 min, confirming that the generation of ¹O₂ is attributed to
470 the presence of the MOF. To exclude time-degradation effects, the absorption spectra

471 of DPBF co-incubated with GelMA/MOF₁ hydrogel in dark condition were recorded
472 and reported in Fig. S7a. The absorbance at 415 nm remains stable after 5 min co-
473 incubation, confirming that the degradation can be related only by the generation of
474 ¹O₂ in MOF, activated by light irradiation. Furthermore, to investigate the possible
475 release of the MOF crystals from the network, the printed hydrogels were sonicated in
476 PBS at 37 °C for 1 h, and the leakage was then detected collecting UV-vis spectra. As
477 shown in Fig. S7b, no characteristic absorption peaks of MOF were observed in any
478 group after 1 hour of sonication. The inset of the same figure also showed that all
479 hydrogels were not damaged during the swelling, while the supernatant remained
480 clear and transparent. Thus, it could be inferred that the MOF crystals are effectively
481 embedded in GelMA matrix, even after swelling. In order to test the stability of
482 photodynamic activity, ¹O₂ detection was repeated after 30 min of exposure to visible
483 light (~30 mW/cm²) on these GelMA/MOF hydrogels, as shown by the fitting curves
484 of ¹O₂ yield in Fig. S8. All the GelMA/MOF hydrogels still exhibited photodynamic
485 activity consistent with previous findings, although their ¹O₂ generation efficiency
486 slightly decreased, while obviously GelMA didn't show any activity. This
487 demonstrates that the embedded MOFs maintain stable and repeatable ¹O₂ generation
488 ^{62,63}. To check whether the radical generation modifies the polymeric networks, DMA
489 tests were repeated on these light-exposed hydrogels. As shown in Fig. S9, the storage
490 moduli of all hydrogels at 37 °C increased compared to pre-exposure values, with
491 more significant increases observed in hydrogels which contain higher amount of
492 MOF. This is can be related to a water loss caused by light exposure, as the storage

493 modulus typically has a negative correlation with the water content of hydrogels ⁶⁴.
 494 On the other hand, it is not possible to exclude that the radicals' generation can also
 495 slightly modify the polymeric network, creating new cross-linking point which can be
 496 consistent with an increase of the moduli. To better evaluate this aspect specific
 497 ageing tests should be performed, which are beyond the scope of this manuscript and
 498 will be better investigated in future activities.



499

500 Fig. 6. (a-e) Digital images and surface thermal under visible illumination (~30

501 mW/cm²) for 180 s. (f) Temperature rise curves. (g-k) UV-vis spectra of DPBF under

502 illumination (520 nm) in presence of GelMA and GelMA/MOF hydrogels. (l) Linear
503 fitting of $^1\text{O}_2$ yields.

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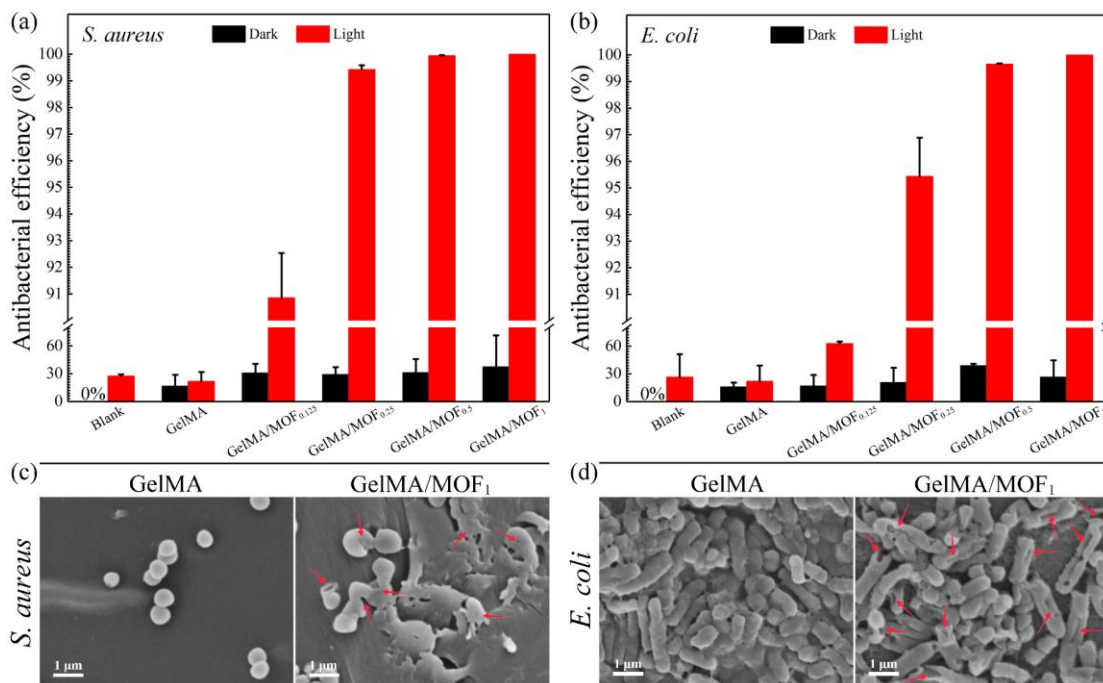
505 3.5. Antibacterial efficacy

506 Based on the above results, it was natural thinking that after incorporating a
507 greater amount of MOF into the GelMA hydrogel, the photothermal and
508 photodynamic abilities could be enhanced simultaneously. Herein, two common
509 strains (*S. aureus* and *E. coli*), which are responsible for most wound infections, were
510 used to evaluate the antibacterial performance of the printed GelMA/MOF hydrogels
511 ⁶⁵. The bacterial suspensions without contacting printed hydrogels were set as blank
512 groups. Fig. S10a and b displayed the surviving bacterial colonies of *S. aureus* and *E.*
513 *coli* on LB agar plates, respectively. In comparison to the blank groups (dark and
514 light), a minimal decrease in bacterial survival could be observed after the bacterial
515 suspensions were exposed to the light illumination alone, indicating that the light
516 caused almost no damage to the bacteria. In the dark groups, both *S. aureus* and *E.*
517 *coli* grew quite well after contacting with GelMA and GelMA/MOF hydrogels for 30
518 min. However, under light illumination, the viable colonies of both types of bacteria
519 decreased as the MOF content increased in the GelMA/MOF hydrogels. This
520 phenomenon demonstrates that GelMA/MOF hydrogels could effectively eliminate
521 bacteria upon light irradiation, and the antibacterial efficiency increases together with
522 the MOF content. The quantified antibacterial efficiencies against *S. aureus* and *E.*
523 *coli* were displayed in Fig. 7a and b, respectively. The light alone caused a 27.29%

524 reduction against *S. aureus* and a 26.35% reduction against *E. coli*, which could be
525 considered negligible in terms of bactericidal effect³⁸. Additionally, all the dark
526 groups displayed slight reduction against *S. aureus* and *E. coli*, which could be
527 attributed to the bacterial adhesion on GelMA or GelMA/MOF hydrogels, rather than
528 a bactericidal action. After the hydrogels were illuminated under light, GelMA/MOF₁
529 hydrogel exhibited the highest antibacterial efficiency against *S. aureus* (> 99.99%)
530 and *E. coli* (> 99.99%), followed by GelMA/MOF_{0.5} (*S. aureus*: 99.94%, *E. coli*:
531 99.65%), GelMA/MOF_{0.25} (*S. aureus*: 99.42%, *E. coli*: 95.43%), GelMA/MOF_{0.125} (*S.*
532 *aureus*: 90.85%, *E. coli*: 62.54%), and GelMA (*S. aureus*: 21.67%, *E. coli*: 21.90%).
533 Here, the slight reduction observed in GelMA hydrogels against both *S. aureus* and *E.*
534 *coli* also could be attributed to bacterial adhesion rather than sterilization. The results
535 of the antibacterial tests are consistent with the findings of the
536 photothermal/photodynamic analysis.

537 SEM was also employed to observe the morphologies of bacteria after treatment
538 with GelMA/MOF hydrogels. Herein, bacteria were inoculated on GelMA and
539 GelMA/MOF_x hydrogels and illuminated for 30 min for comparison. As shown in Fig.
540 7c, *S. aureus* exhibited typical morphologies with intact spherical shapes and smooth
541 surfaces on GelMA hydrogel. However, on GelMA/MOF₁ hydrogel, the membranes
542 of *S. aureus* were severely deformed and ruptured (red arrows). The same
543 phenomenon could be observed in Fig. 7b, where *E. coli* maintained their typical and
544 intact rod shapes on GelMA hydrogel, while appearing wrinkled and ruptured on
545 GelMA/MOF₁ hydrogel (red arrows). Additionally, the bacteria treated with

546 GelMA/MOF_{0.125}, GelMA/MOF_{0.25}, and GelMA/MOF_{0.5} hydrogels are shown in Fig.
 547 S11. The morphological deformation of *S. aureus* and *E. coli* is also observed, with
 548 the degree becoming more pronounced as the MOF content increases. Thus, the
 549 bactericidal action of the GelMA/MOF hydrogels could be ascribed to a synergism of
 550 MOF-triggered photothermal and photodynamic processes. This combined effect can
 551 disrupt the structure of the bacterial membrane, leading to the outflow of intracellular
 552 substances and ultimately triggering apoptosis^{66, 67}.



553
 554 Fig. 7. Antibacterial efficiencies of GelMA and GelMA/MOF hydrogels against *S.*
 555 *aureus* (a) and *E. coli* (b). SEM images of *S. aureus* (c) and *E. coli* (d) contacted with
 556 GelMA and GelMA/MOF₁ under visible light for 30 min irradiation.

557

558 3.6. Hemocompatibility and cytocompatibility

559 An ideal medical dressing should be biocompatible with both blood cells and
 560 skin tissue cells⁶⁸. Here, *in vitro* hemolysis and cytotoxicity assays were conducted to

561 evaluate the biocompatibilities of printed GelMA/MOF hydrogels. As depicted in Fig.
562 8a, the hemolysis ratios of GelMA and GelMA/MOF hydrogels remained below the
563 specified limit (5% hemolysis) after 3-hour co-incubation, indicating their good
564 compatibility with blood cells ⁶⁹. The inset in Fig. 8a illustrates the supernatants of
565 each group, where RBCs ruptured after incubation in DI water (positive control),
566 leading to a bright red in the supernatant. Conversely, the RBCs co-incubated with
567 GelMA and GelMA/MOF hydrogel exhibited supernatants that appeared nearly
568 colorless and transparent, like the incubation in PBS (negative), indicating
569 insignificant levels of hemolysis. Fig. 8b displays the cytocompatibility of printed
570 GelMA and GelMA/MOF hydrogels. After a 48 h co-culture with L929 cells, the cell
571 viability in all sample groups exceeded 80%, confirming the low cytotoxicity of these
572 GelMA/MOF hydrogels ⁷⁰. The Live/Dead staining assay was also performed to
573 assess the condition of L929 cells following the cytotoxicity test. As shown in Fig. 8c,
574 the majority of spindle-shaped cells exhibited green fluorescence in negative control
575 and all hydrogel groups, corresponding to the living cells. Few dead cells,
576 characterized by red fluorescence and a globular shape, were observed in these groups,
577 suggesting negligible cytotoxicity. The results of *in vitro* hemolysis and cytotoxicity
578 assays demonstrate the favorable biocompatibility of printed GelMA/MOF hydrogels,
579 positioning them as promising candidates for use in wound dressings.

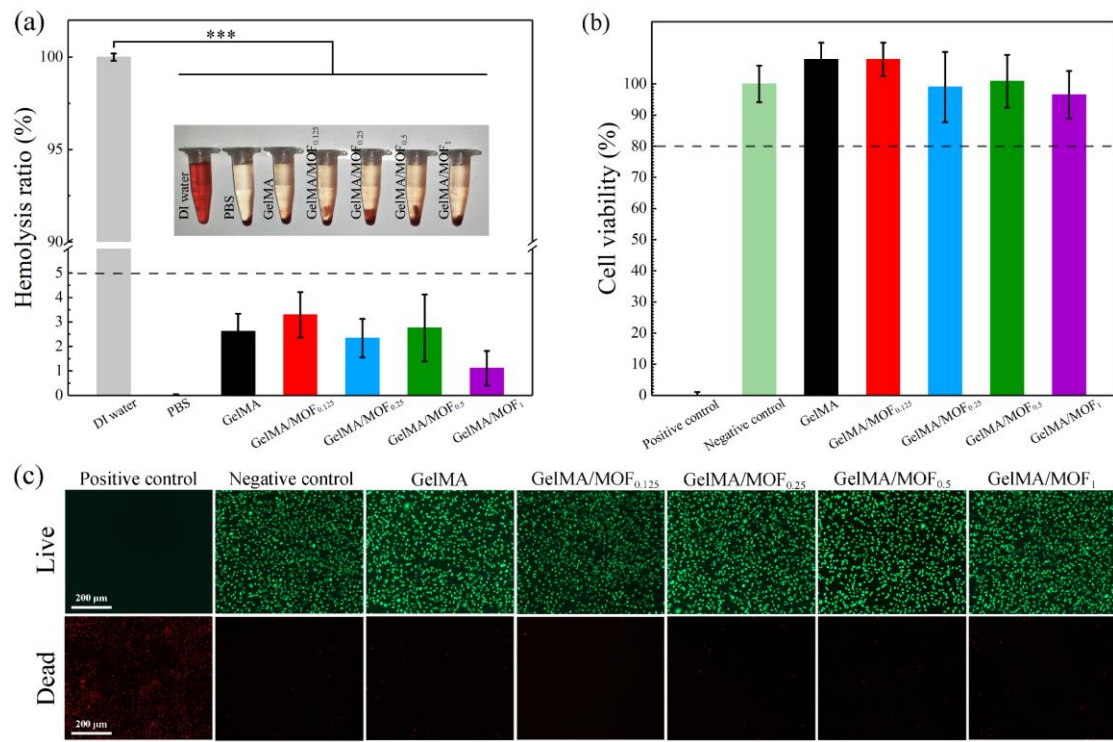


Fig. 8. (a) Hemolysis assay. (b) Cell viability of cytotoxicity assay. (c) Live/Dead staining assay. (***) represents $P < 0.001$.

4. Conclusions

In summary, this work reports the fabrication of printable MOF-based nanocomposite hydrogels through DLP 3D printing, utilizing photocurable GelMA resins and incorporating PCN-224 as a nanofiller. During the printing, higher UV-light intensity and longer slicing time were required due to the photo-competitive effect of the MOF, while the printing precision could be improved. This facilitates the construction of more intricate and fidelity hydrogel structures tailored to clinical wound defects. Moreover, the incorporation of MOF imparts photothermal and photodynamic properties to the printed hydrogels, with both effects amplifying as MOF concentration increases. However, a high concentration of MOF affects printing

594 and the mechanical properties of the nanocomposite hydrogels. The result of
595 antibacterial assay revealed an enhancement in antibacterial performance with
596 increasing MOF concentration, with GelMA/MOF₁ exhibiting the highest
597 antibacterial efficiency against *S. aureus* (> 99.99%) and *E. coli* (> 99.99%) for 30
598 min illumination, followed by GelMA/MOF_{0.5} (*S. aureus*: 99.94%, *E. coli*: 99.65%),
599 GelMA/MOF_{0.25} (*S. aureus*: 99.42%, *E. coli*: 95.43%), and GelMA/MOF_{0.125} (*S.*
600 *aureus*: 90.85%, *E. coli*: 62.54%). Additionally, all printed GelMA/MOF hydrogels
601 demonstrated excellent cytocompatibility and hemocompatibility. Therefore, utilizing
602 MOF as a functional filler in the preparation of biocompatible
603 photodynamic/photothermal hydrogels through DLP 3D printing not only mitigates
604 the risks associated with MOF drug residue but also allows for the customization of
605 wound dressings matching specific skin defects. In the next future, this additive
606 approach will hold significant clinical relevance in light therapy.

607

608 **Declaration of competing interest**

609 The authors declare no competing financial interest.

610

611 **Supporting Information**

612 Preliminary 3D printing experiments 3D printed parts with increasing content of
613 MOFs, 3D printing working curves, evaluation of 3D printing fidelity, additional
614 SEM experiments on freeze-dried matrices, degradation test, leakage test, evaluation
615 of ¹O₂ yields after ageing, DMA measurements after UV ageing, additional bacterial
616 test and additional SEM images of bacteria are supplied as Supporting Information.

617

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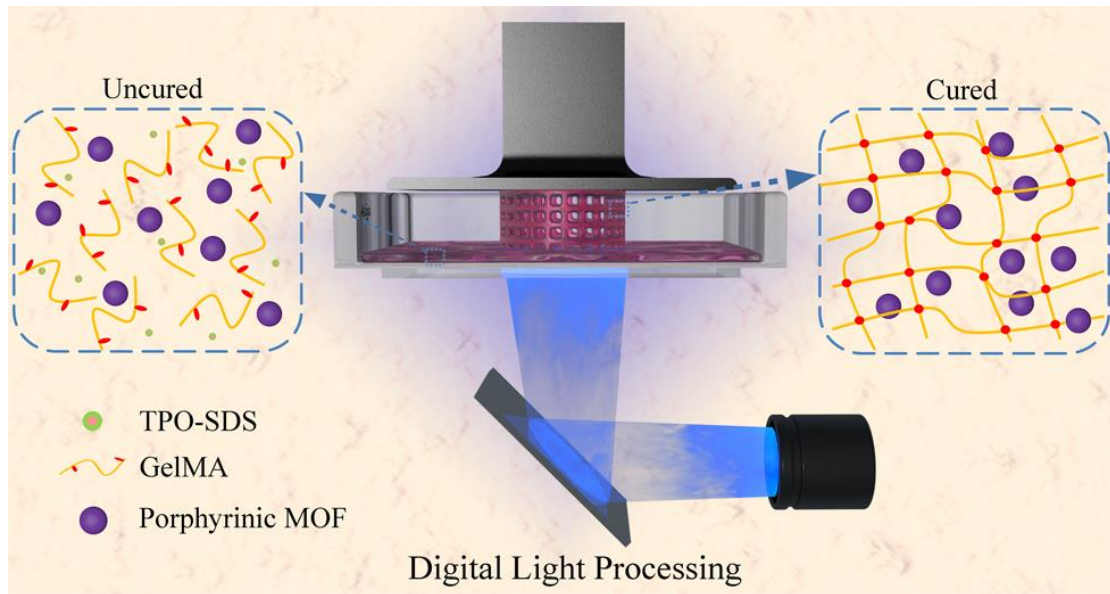
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817 **Table Of Contents (TOC)**

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