Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Self-Healing Hydrogels Triggered by Free Amino Acids

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Contents

Materials - All chemicals and solvents were purchased by Sigma-Aldrich, VWR or Iris Biotech and used as received. Acetonitrile was distilled under inert atmosphere before use. MilliQ water (Millipore, resistivity = 18.2 mΩ.cm) was used throughout.

Synthesis of $CH_2(C_3H_6CO\text{-}L\text{-}Phe\text{-}D\text{-}Oxd\text{-}OBn)_2$ - A solution of Boc-L-Phe-D-Oxd-OBn [1] (2 mmol, 0.96 g) and TFA (36 mmol, 2.78 mL) in dry methylene chloride (20 mL) was stirred at room temperature for 4 hours, then the volatiles were removed under reduced pressure and the corresponding amine salt was obtained pure in quantitative yield without further purification.

A solution of azelaic acid (0.98 g, 0.52 mmol) and HBTU (0.4 mg, 1.04 mmol) in dry acetonitrile (22 mL) was stirred under nitrogen atmosphere for 10 minutes at room temperature. Then a mixture of the previously obtained amine salt (1.04 mmol) and Et_3N (3.2 mmol, 0.47 mL) in dry acetonitrile (15 mL) was added dropwise at room temperature. The solution was stirred for 40 minutes under nitrogen atmosphere, then acetonitrile was removed under reduced pressure and replaced with ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 x 30 mL), and with 5% (w/v) aqueous $NaHCO_3$ (1 x 30 mL), dried over sodium sulphate and concentrated *in vacuo*. The product was obtained pure after silica gel chromatography (DCM 100% → DCM/ethyl acetate 80:20 as eluant) in 64% (1.17 g) overall yield. M.p. = 207 °C; $[\alpha]_D^{20}$ 45.0° (c 0.1, $CHCl_3$); IR (CH_2Cl_2, 3 mM): ν 3428, 1789, 1754, 1707, 1672 cm^{-1}; IR (1% in dry KBr): ν 3309, 1793, 1765, 1736, 1708, 1650 cm^{-1}; ^1H NMR (DMSO, d_6, 300 MHz): δ 0.95-1.18 (m, 10H, $CH_2(CH_2)_5CH_2$), 1.20–1.40 (m, 4H, $CH_2(CH_2)_5CH_2$), 1.50 (d, 6H, *J* = 6.3 Hz, $OCHCH_3$), 2.00 (m, 4H, CH_2CO), 2.70 (dd, 2H, *J* = 10.8, 13.5 Hz, CHN-CHH-Ph), 3.10 – 3.20 (dd, 2H, *J* = 3.3, 13.5 Hz, CHN-CHH-Ph), 4.65 (d, 2H, *J* = 4.2 Hz, CHN), 4.80– 4.90 (m, 2H, OCH), 5.18 (d, 2H, *J* = 12.3 Hz, OCHHPh), 5.25 (d, 2H, *J* = 12.6 Hz, OCHHPh), 5.8 (m, 2H, CHN-CH_2Ph), 7.20– 7.40 (m, 20H, 4 x Ph), 8.25 (d, 2H, *J* = 8.7 Hz, NH); ^{13}C NMR (DMSO,d_6, 75 MHz): δ 14.8, 15.3, 21.1, 25.9, 29.0, 35.7, 37.7, 38.5, 51.0, 53.1, 55.4, 62.0, 67.7, 74.3, 127.2, 128.6, 128.8, 128.9, 129.2, 129.8, 136.0, 138.0, 152.5, 168.6, 172.7, 173.2.

(1) Angelici, G.; Falini, G.; Hofmann, H.-J.; Huster, D.; Monari, M.; Tomasini, C. *Angew. Chemie Int. Ed.* **2008**, *47* (42), 8075.

Synthesis of $CH_2(C_3H_6CO\text{-}L\text{-}Phe\text{-}D\text{-}Oxd\text{-}OH)_2$ A

$CH_2(C_3H_6CO\text{-}L\text{-}Phe\text{-}D\text{-}Oxd\text{-}OBn)_2$ (1 mmol, 0.92 g)) was dissolved in MeOH (35 mL) under nitrogen. C/Pd (50 mg, 10% w/w) was added under nitrogen. Vacuum was created inside the flask using the vacuum line. The flask was then filled with hydrogen using a balloon (1 atm). The solution was stirred for two hours under a hydrogen atmosphere. The product was obtained pure in quatitative yield (0.73 g) after filtration through a celite pad using ethyl acetate and concentration *in vacuo*.

M.p. = 201 °C; $[\alpha]_D^{20}$ -36.0 (c 1.2, MeOH); ^{1}H NMR (CD_3OD, 400 MHz): δ 1.06-1.47 (m, 10H, $CH_2(CH_2)_5CH_2$), 1.58 (d, 6H, *J* = 6.4 Hz, OCHCH_3), 2.03-2.15 (m, 4H, $CH_2(CH_2)_5CH_2$), 2.91 (dd, 2H, *J* = 9.6, 13.6 Hz, CHN-C*H*HPh), 3.14 (dd, 2H, *J* = 5.2, 13.6 Hz, CHN-CH*H*Ph), 4.00 (d, 2H, *J* = 5.6 Hz, C*H*N-CHHPh), 4.62– 4.87 (m, 2H, OC*H*), 5.80 (m, 2H, C*H*N-CH_2Ph), 7.20– 7.40 (m, 20H, 4 x Ph); ^{13}C NMR (CD_3OD, 100 MHz): δ 19.8, 25.3, 28.3, 28.5, 35.2, 37.6, 52.7, 61.7, 74.4, 126.5, 128.0, 129.1, 136.6, 151.1, 153.3, 169.7, 172.7, 174.4.

Table S1. Gelation properties of hydrogels obtained as a function of an increasing amount of gelator **A** and of the different amino acids or of GdL.

Entry	**% Gelator** (w/w)	**Trigger** (equiv.)	**Final pH**	T_{gel} (°C)
1	1	Arg (1)	8.0	80 [a]
2	2	Arg (1)	8.0	98 [a]
3	1	Arg (2)	9.0	73 [a]
4	2	Arg (2)	9.0	88 [a]
5	1	Hys (1)	7.5	84 [a]
6	2	Hys (1)	7.5	100 [c]
7	1	Hys (2)	8.5	86 [a]
8	2	Hys (2)	8.5	97 [a]
9	1	Lys (1)	7.5	60 [b]
10	2	Lys (1)	7.5	95 [b]
11	1	Lys (2)	8.5	87 [b]
12	2	Lys (2)	8.5	91 [b]
13	1	Asp (1)	3.5	53 [b]
14	2	Asp (1)	3.0	63 [b]
15	1	Asp (2)	3.0	50 [b]
16	2	Asp (2)	2.5	58 [b]
17	1	Ala (1)	4.0	25 [c]
18	2	Ala (1)	3.5	34 [c]
19	1	Ala (2)	2.5	80 [c]
20	2	Ala (2)	3.0	94 [c]
21	1	Ser (1)	5.0	34 [a]
22	2	Ser (1)	5.0	65 [a]
23	1	Ser (2)	3.0	34 [a]
24	2	Ser (2)	3.0	60 [a]
25	1	Phe (1)	4.0	43 [a]
26	2	Phe (1)	3.5	45 [c]
27	1	Phe (2)	3.5	40 [c]
28	2	Phe (2)	3.0	48 [c]
29	1	Tyr (1)	4.0	75 [c]
30	2	Tyr (1)	3.5	55 [c]
31	1	Tyr (2)	3.0	75 [c]
32	2	Tyr (2)	3.0	80 [c]
33	1	Trp (1)	6.0	88 [b]
34	2	Trp (1)	4.5	95 [b]
35	1	Trp (2)	3.0	90 [b]
36	2	Trp (2)	2.5	95 [c]
37	1	GdL (2)	3.8	92 [b]
38	2	GdL (2)	4.0	98 [c]

[a] thermoreversible gel; [b] not thermoreversible gel, the gelator melts then precipitate on cooling; [c] the gel does not melt as syneresis occurs on heating.

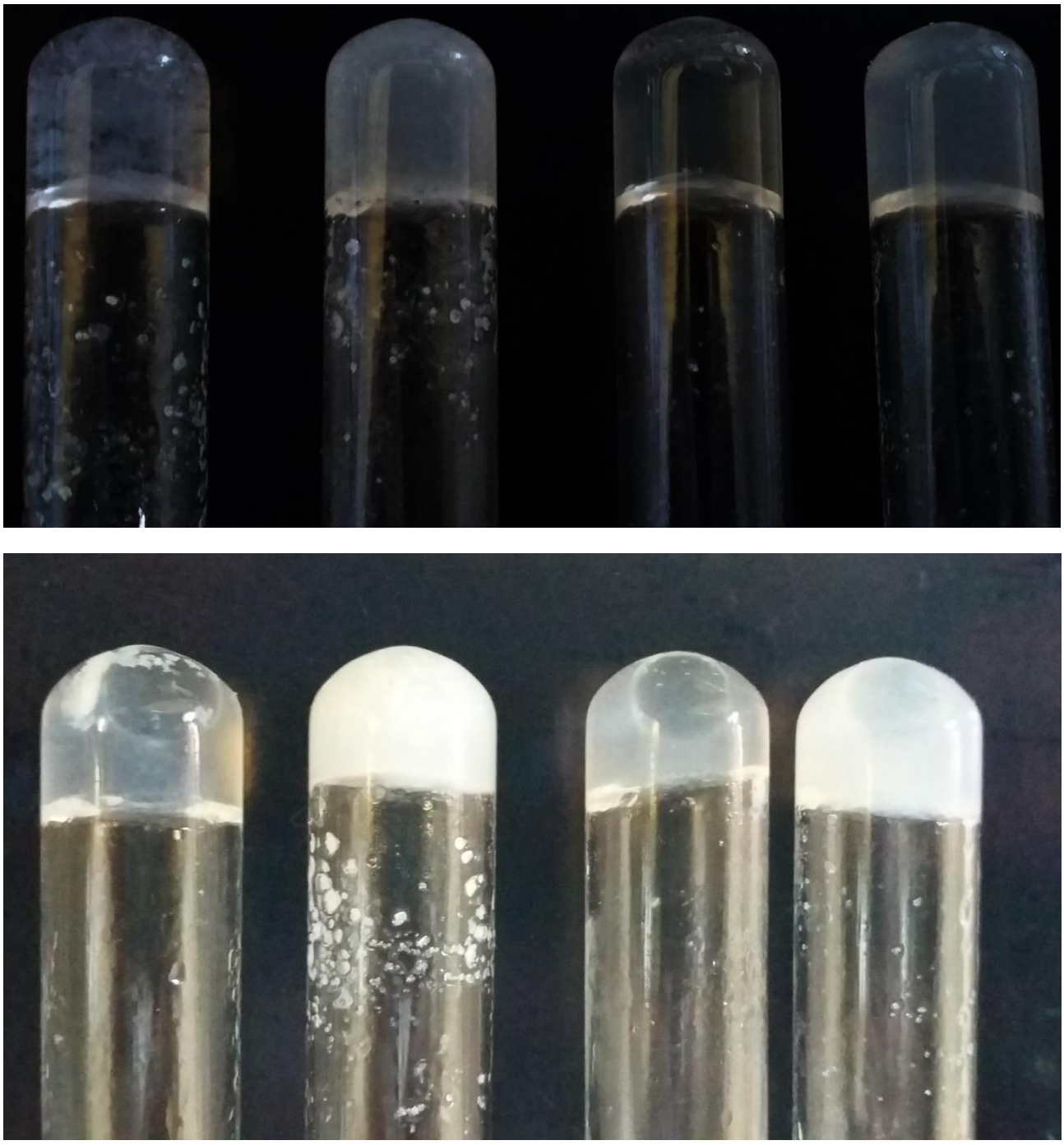


Figure S1. (Top) Photographs of hydrogels prepared with **A** and arginine in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : arginine equiv.). (Bottom) Photograph of the same samples after melting on heating and cooling down. The dropped ball trapped in the gel is clearly visible.

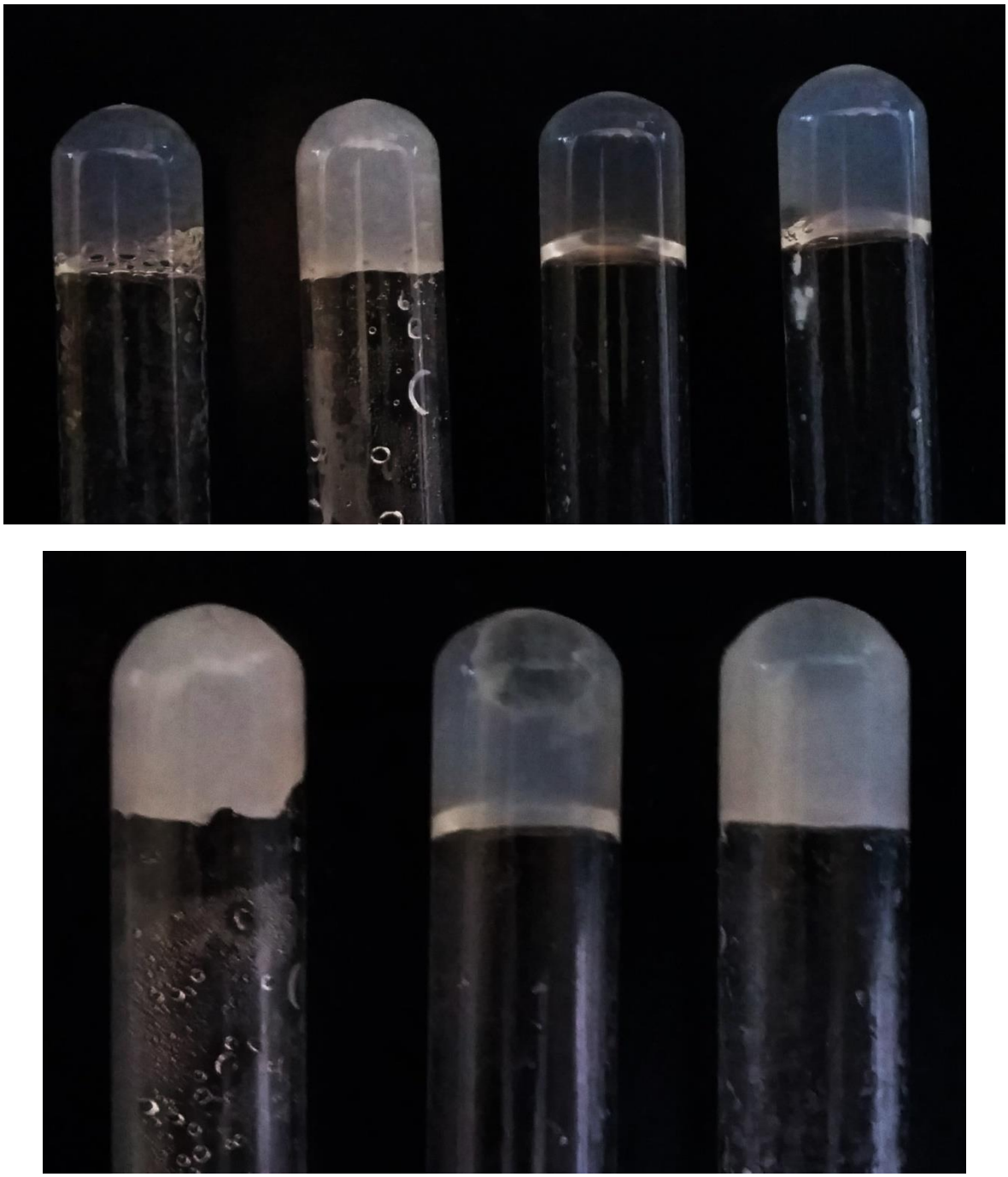


Figure S2. (Top) Photographs of hydrogels prepared with **A** and hystidine in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : hystidine equiv.). (Bottom) Photograph of samples 1:1, 2:1, 2:2 after melting on heating and cooling down. The dropped ball trapped in the gel is clearly visible.

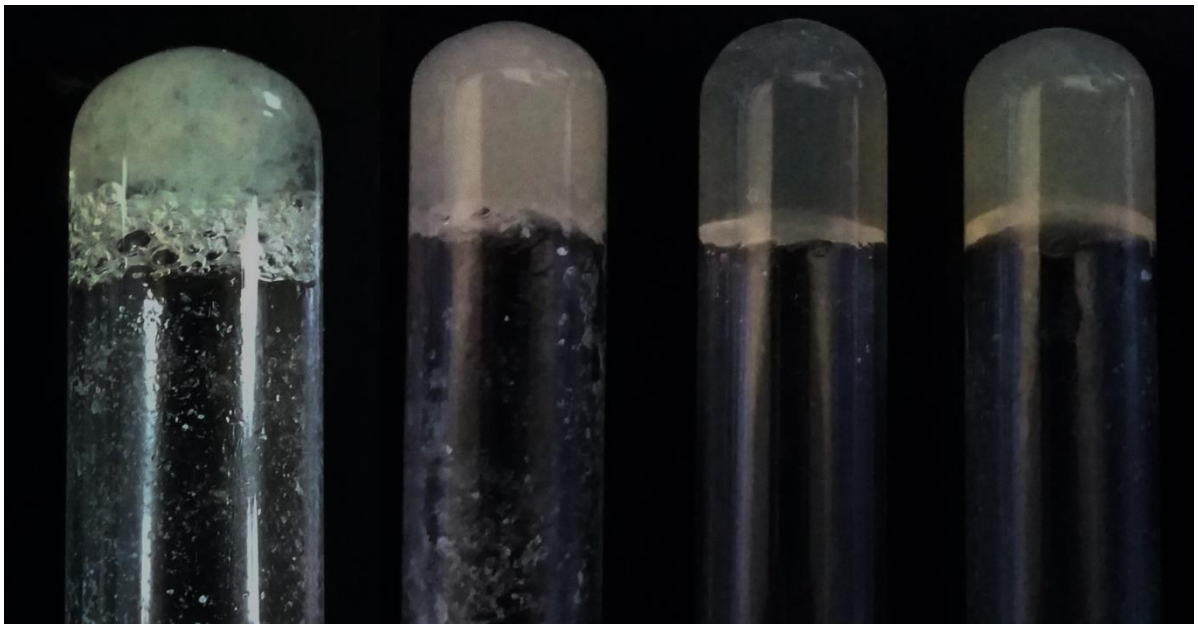


Figure S3. Photographs of hydrogels prepared with **A** and lysine in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : lysine equiv.).

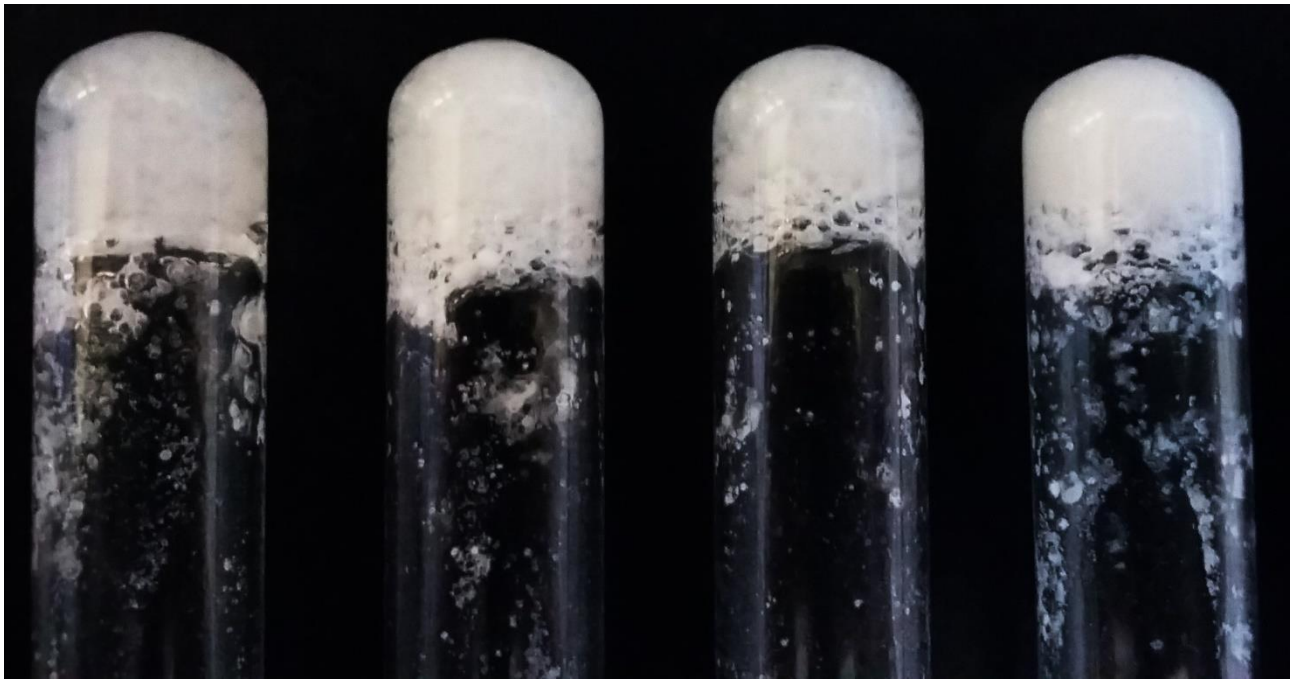


Figure S4. Photographs of hydrogels prepared with **A** and aspartic acid in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : aspartic acid equiv.).

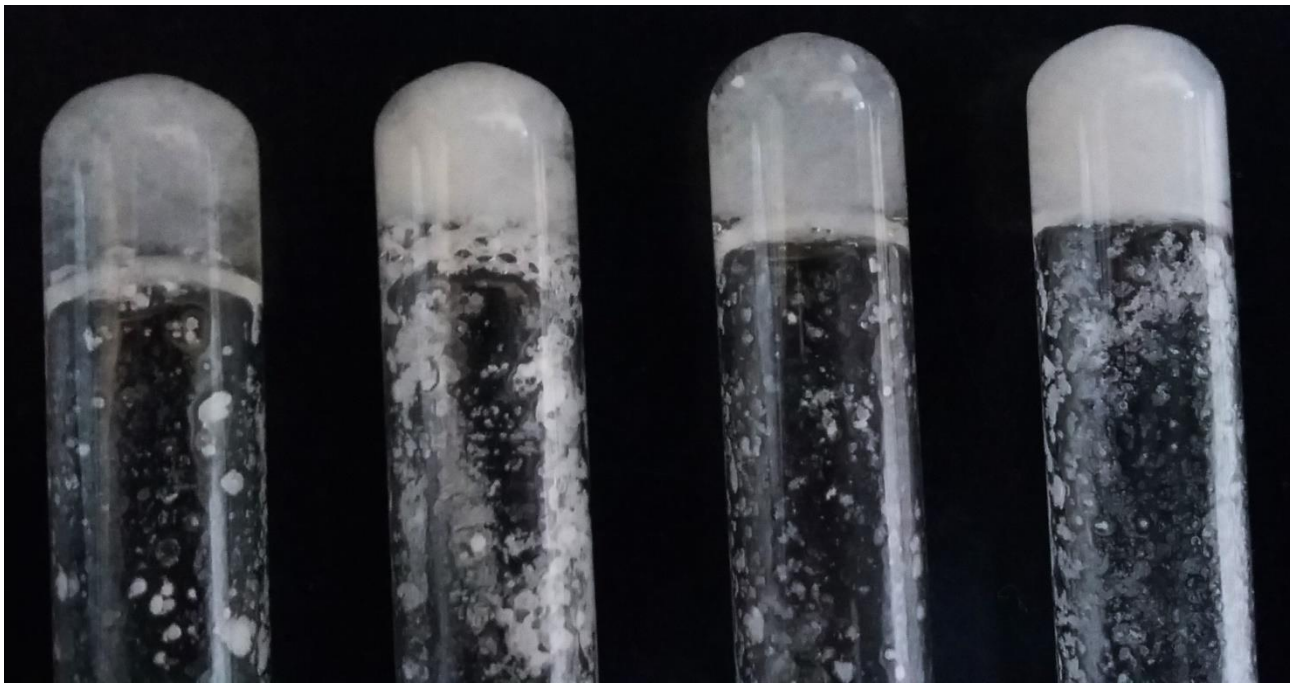


Figure S5. Photographs of hydrogels prepared with **A** and alanine in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : alanine equiv.).

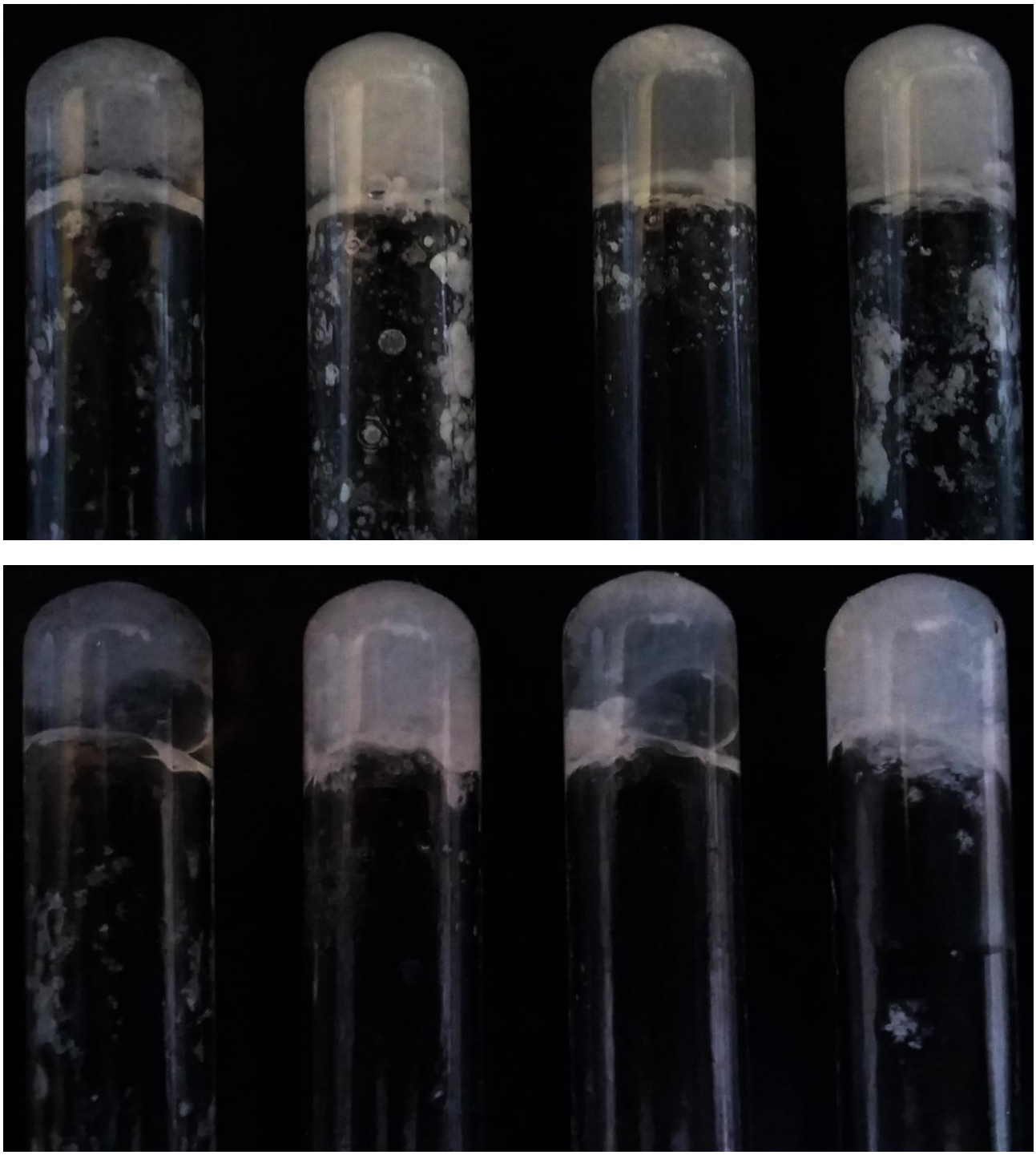


Figure S6. (Top) Photographs of hydrogels prepared with **A** and serine in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : serine equiv.). (Bottom) Photograph of samples 1:1, 2:1, 2:2 after melting on heating and cooling down. The dropped ball trapped in the gel is clearly visible.

Figure S7. Photographs of hydrogels prepared with **A** and phenylalanine in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : phenylalanine equiv.).

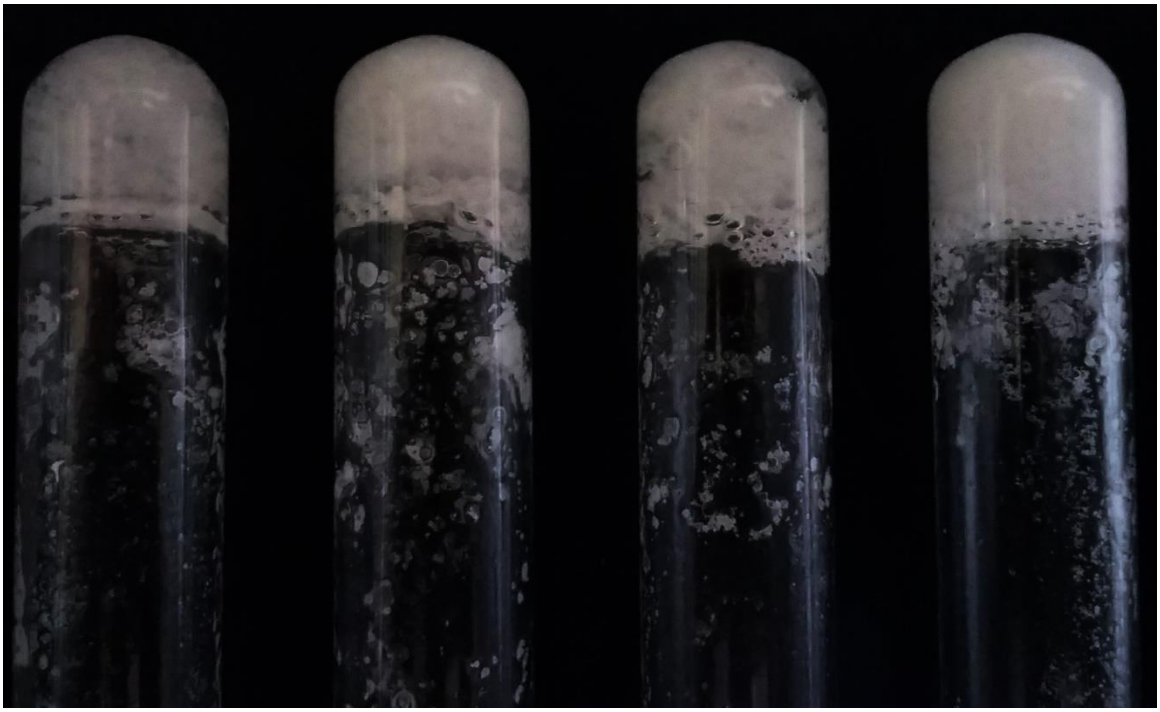


Figure S8. Photographs of hydrogels prepared with **A** and tyrosine in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : tyrosine equiv.).

Figure S9. Photographs of hydrogels prepared with **A** and tryptophan in different concentration. From left to right 1:1, 2:1, 1:2, 2:2 (% w/w : tryptophan equiv.).

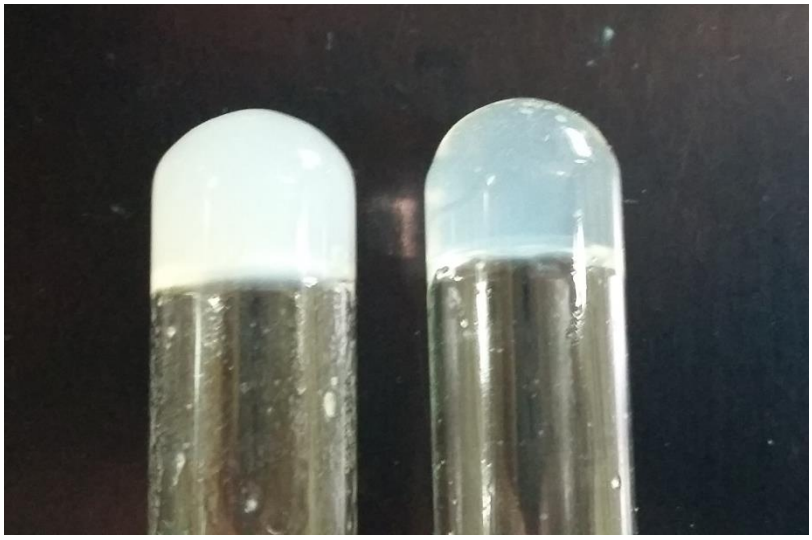


Figure S10. Photographs of hydrogels prepared with **A** in different concentration and gluconolactone (2 equiv.). From left to right 1, 2 (% w/w).

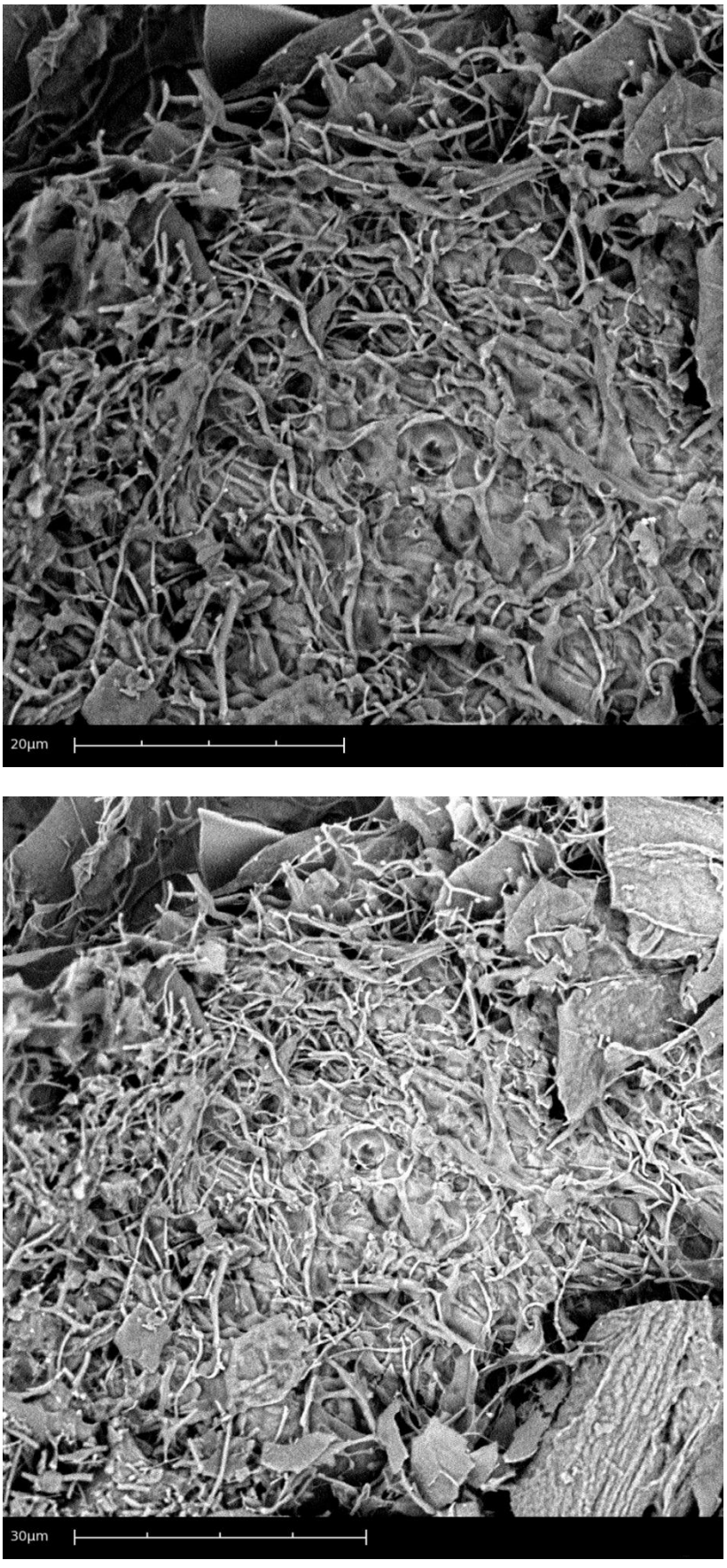
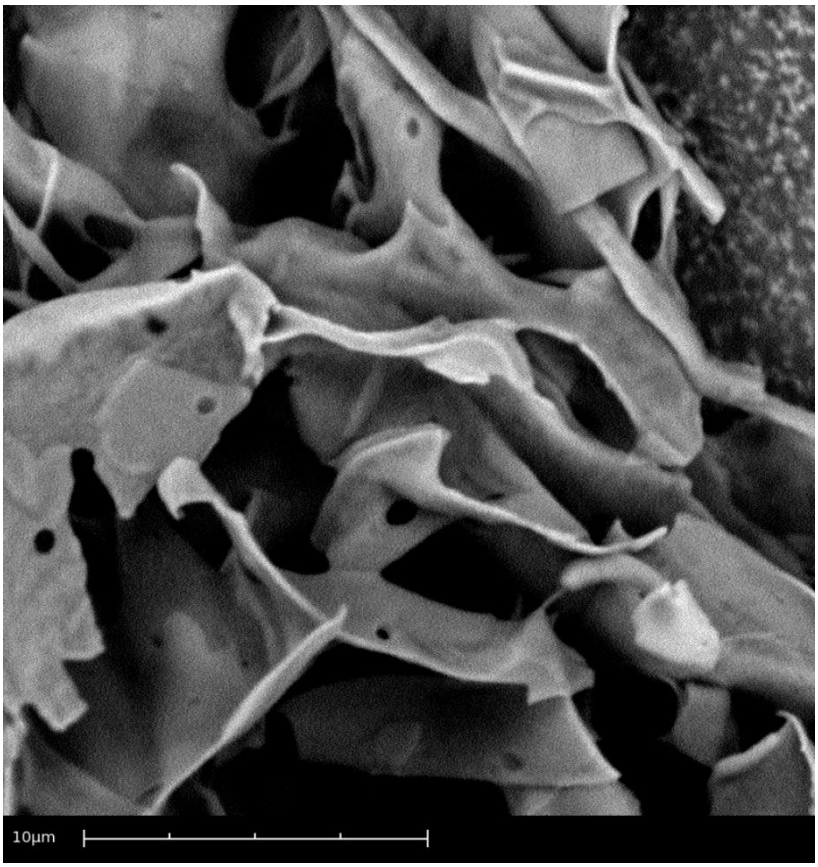


Figure S11. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and arginine (1 equiv.).



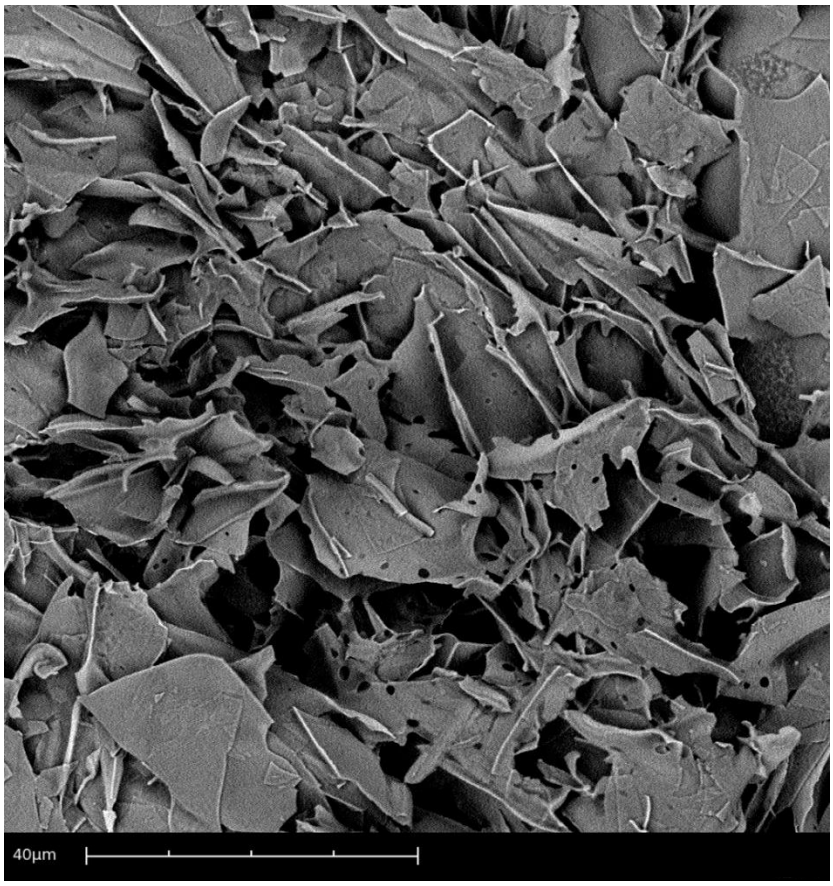


Figure S12. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and arginine (2 equiv.).

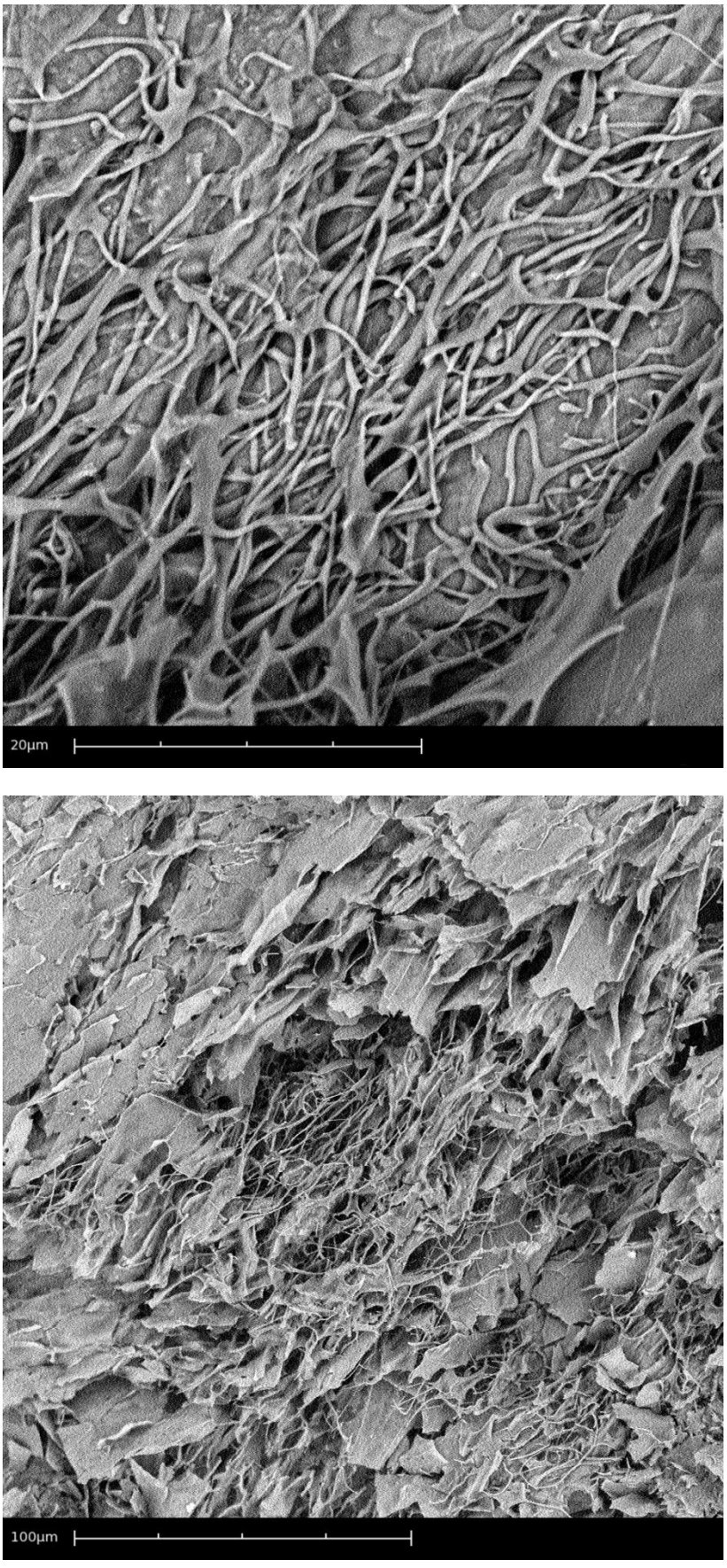


Figure S13. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and hystidine (1 equiv.).

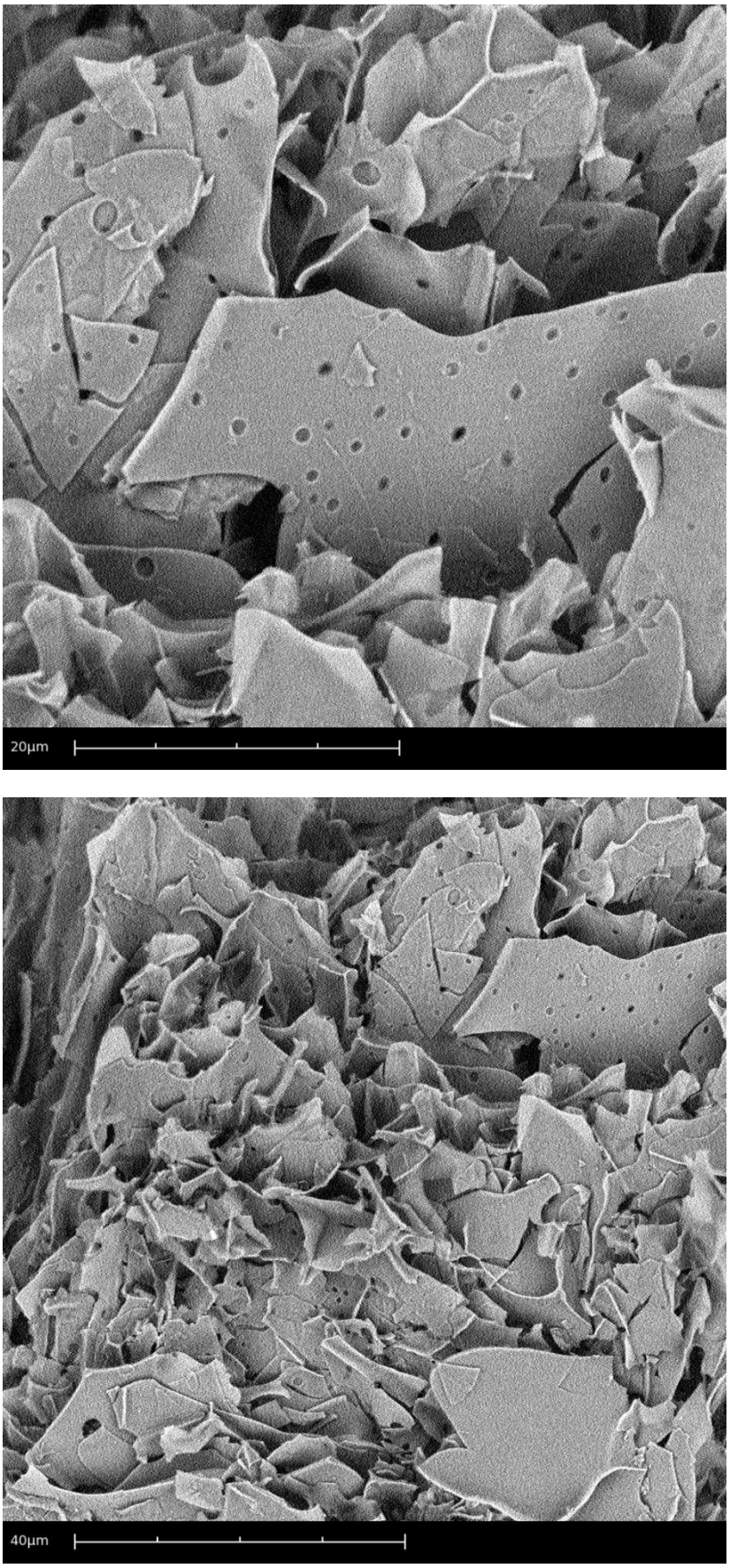


Figure S14. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and hystidine (2 equiv.).

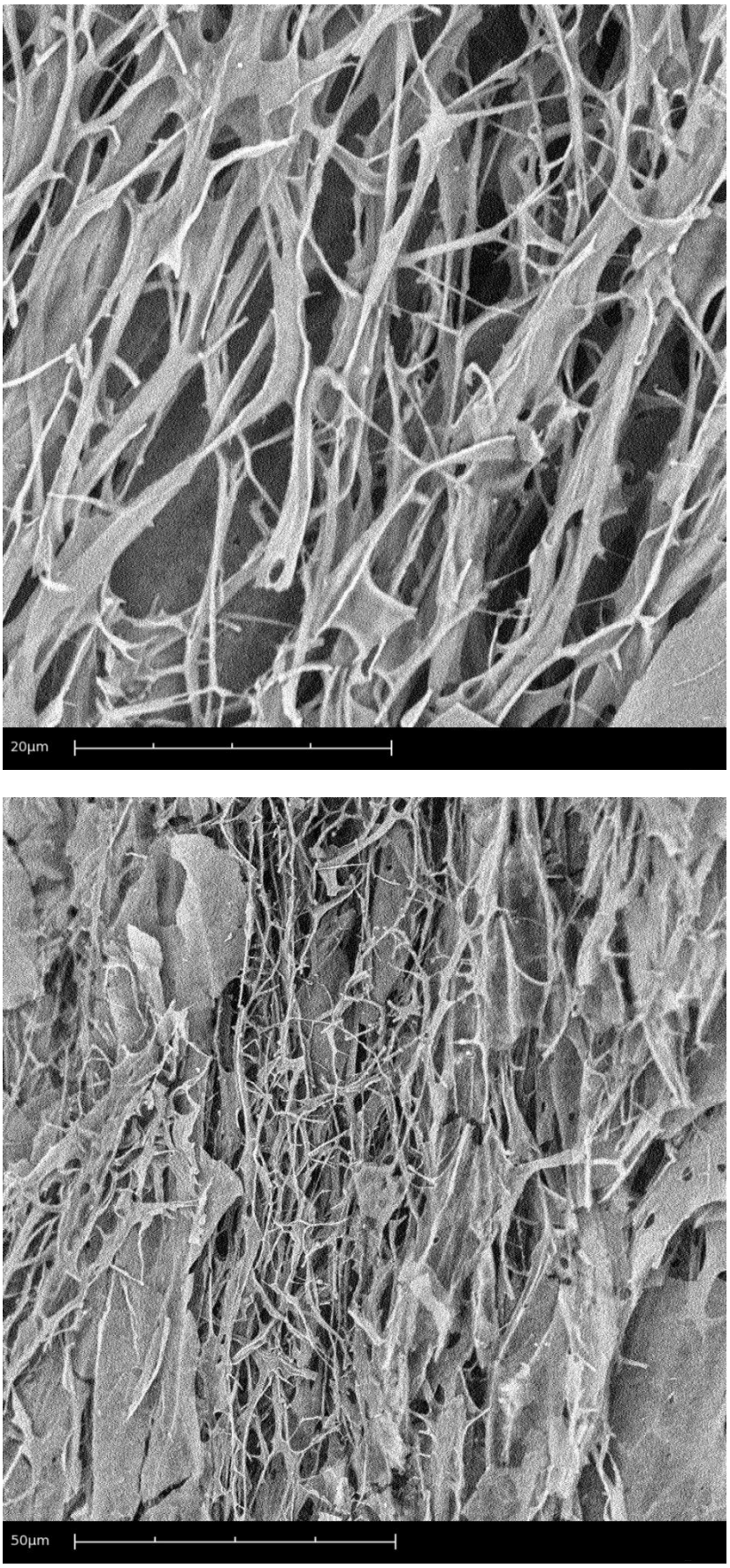


Figure S15. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and lysine (1 equiv.).

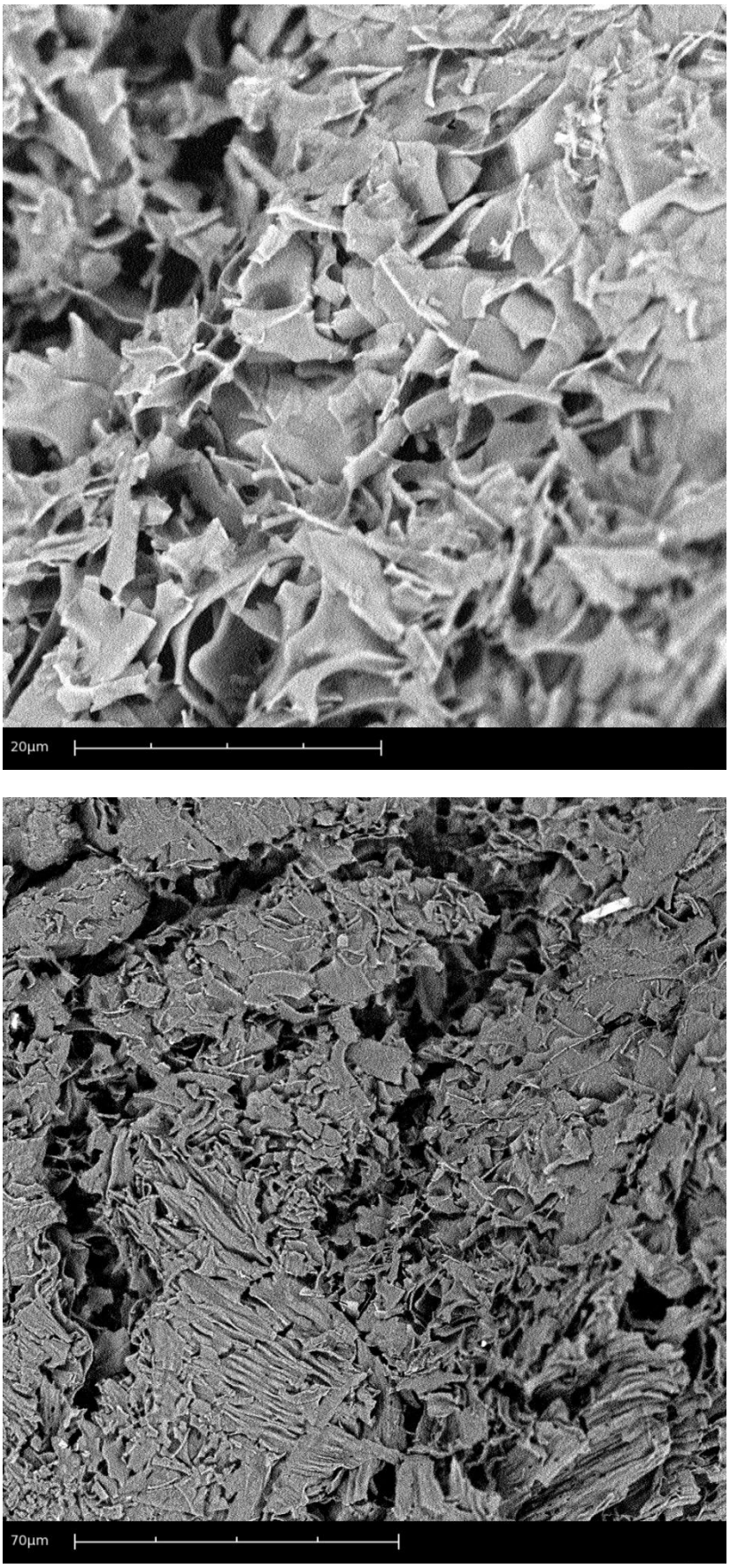


Figure S16. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and lysine (2 equiv.).

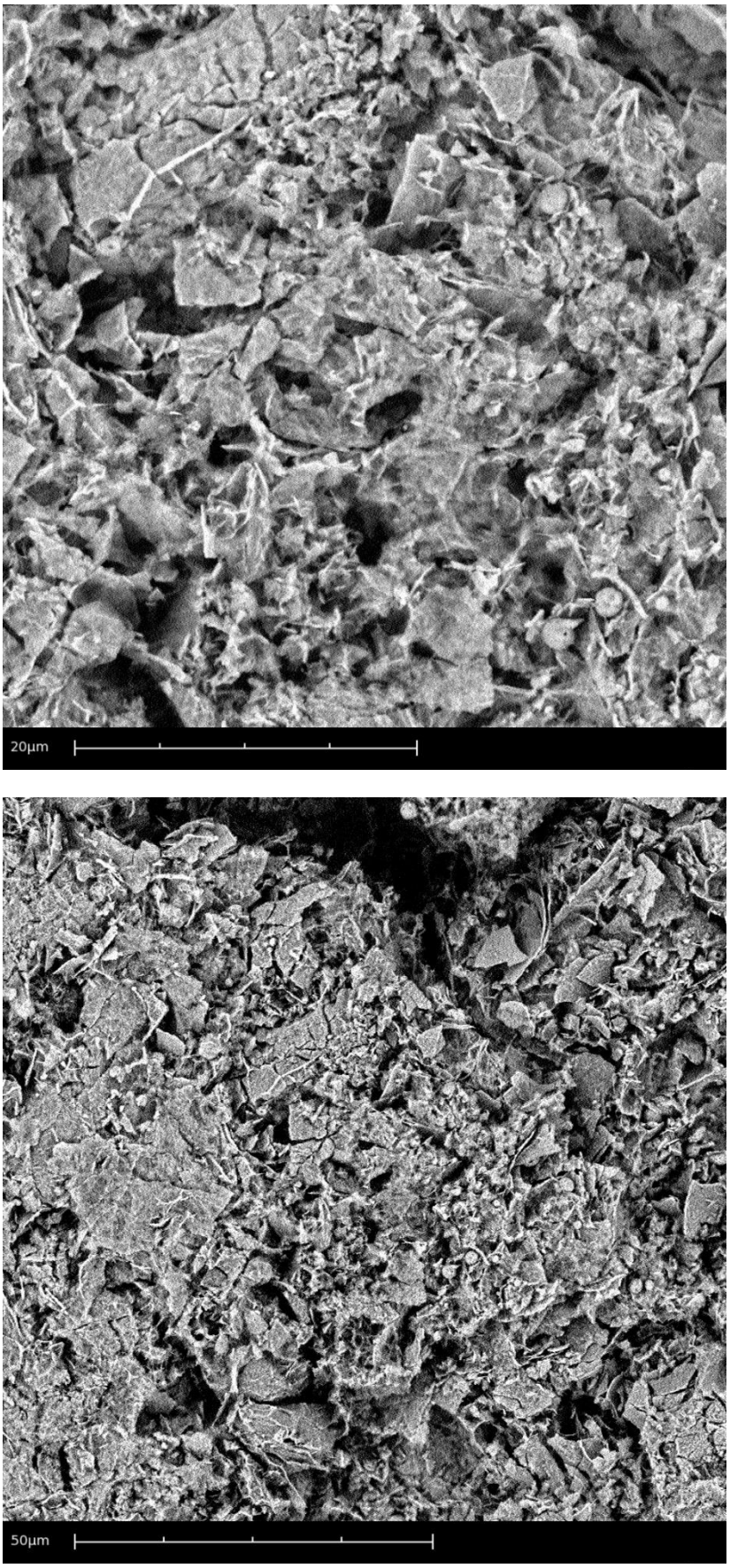


Figure S17. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and aspartic acid (1 equiv.).

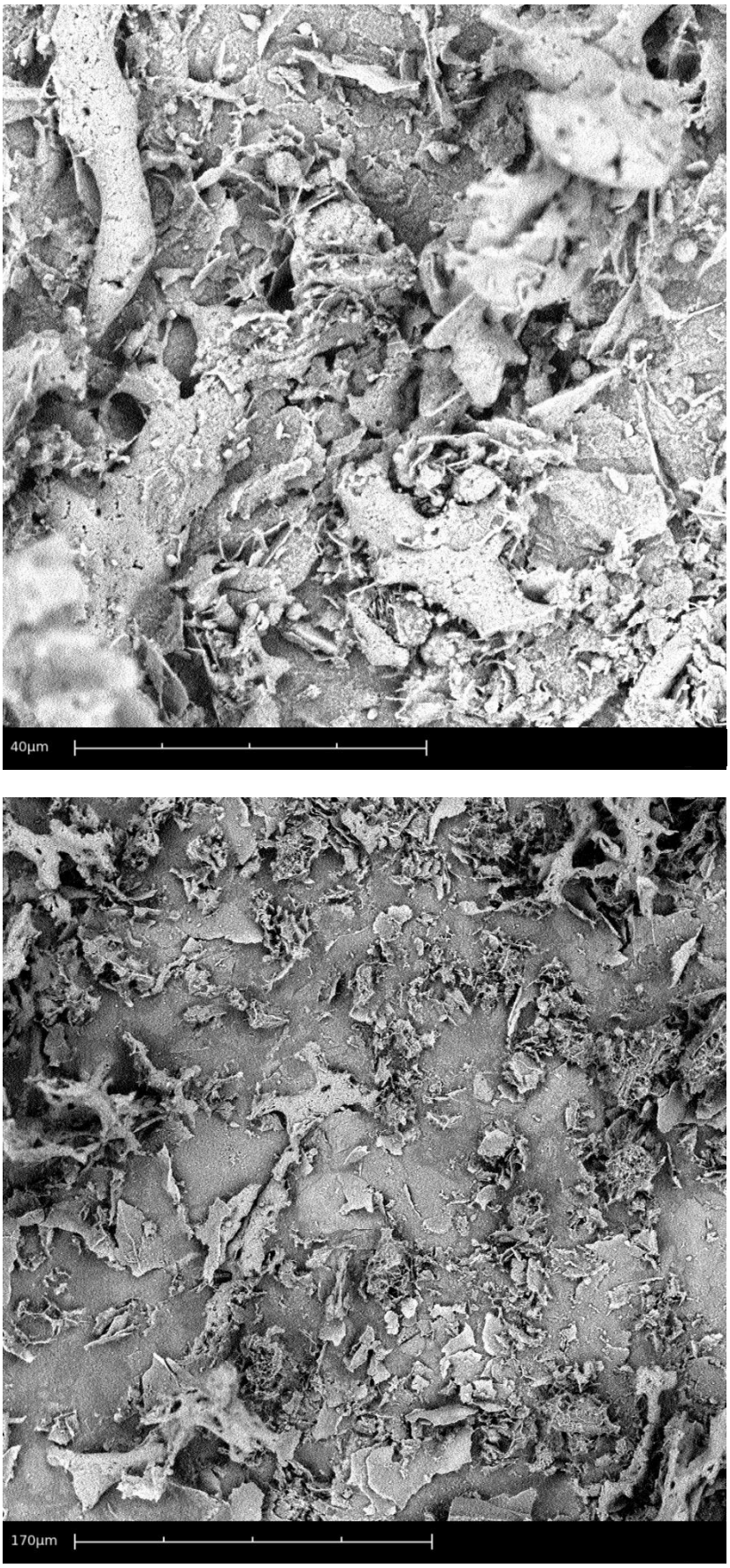


Figure S18. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and aspartic acid (2 equiv.).

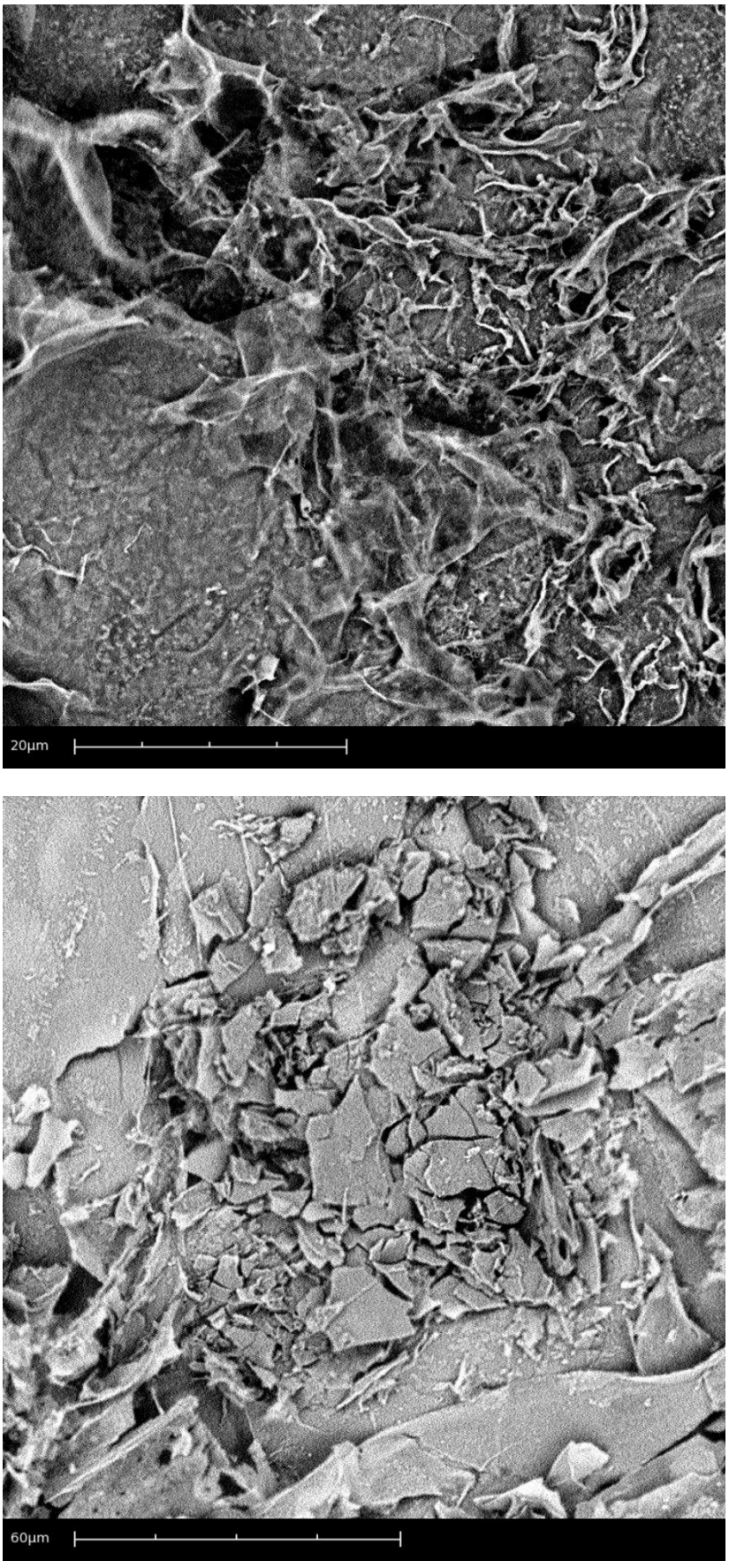


Figure S19. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and serine (1 equiv.).

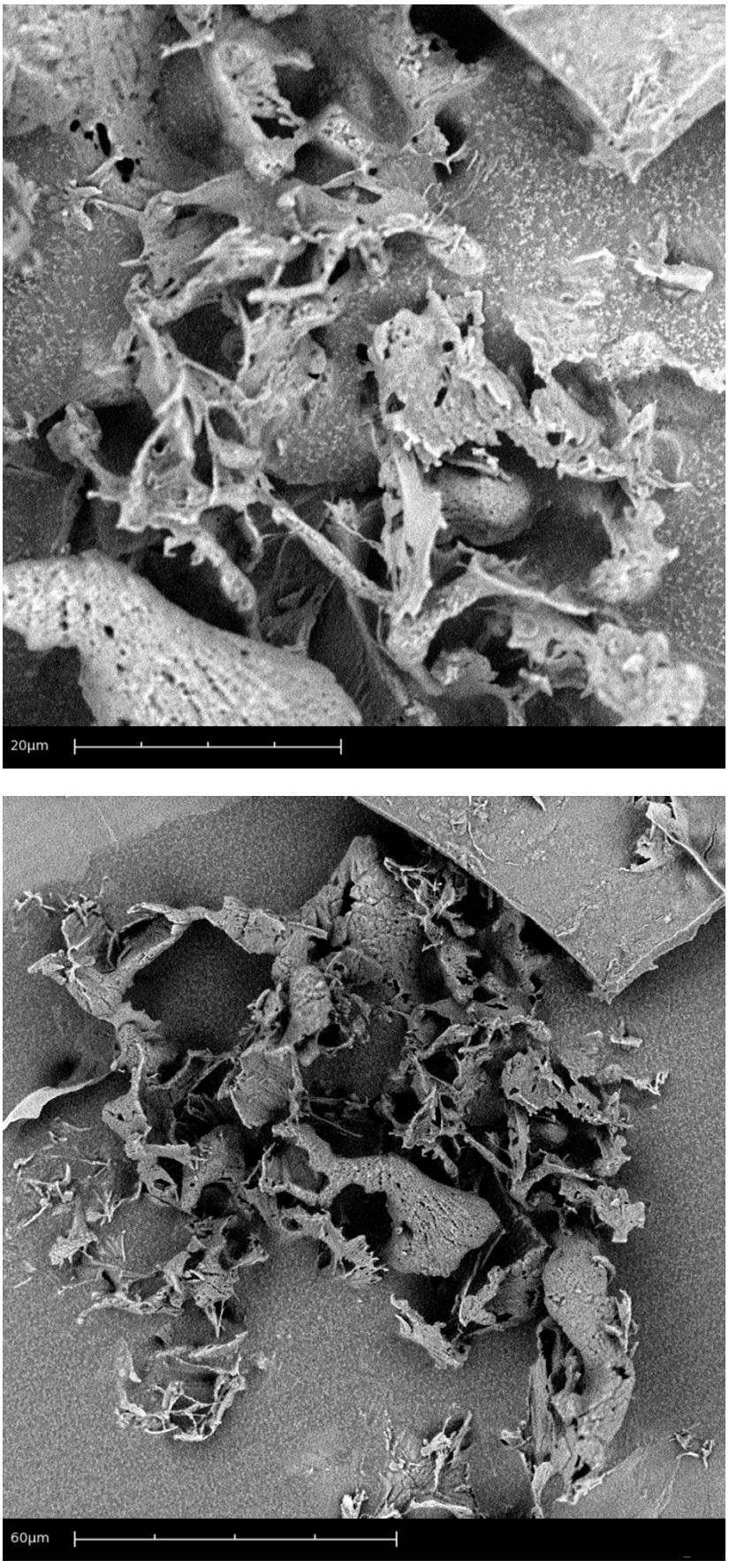


Figure S20. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and serine (2 equiv.).

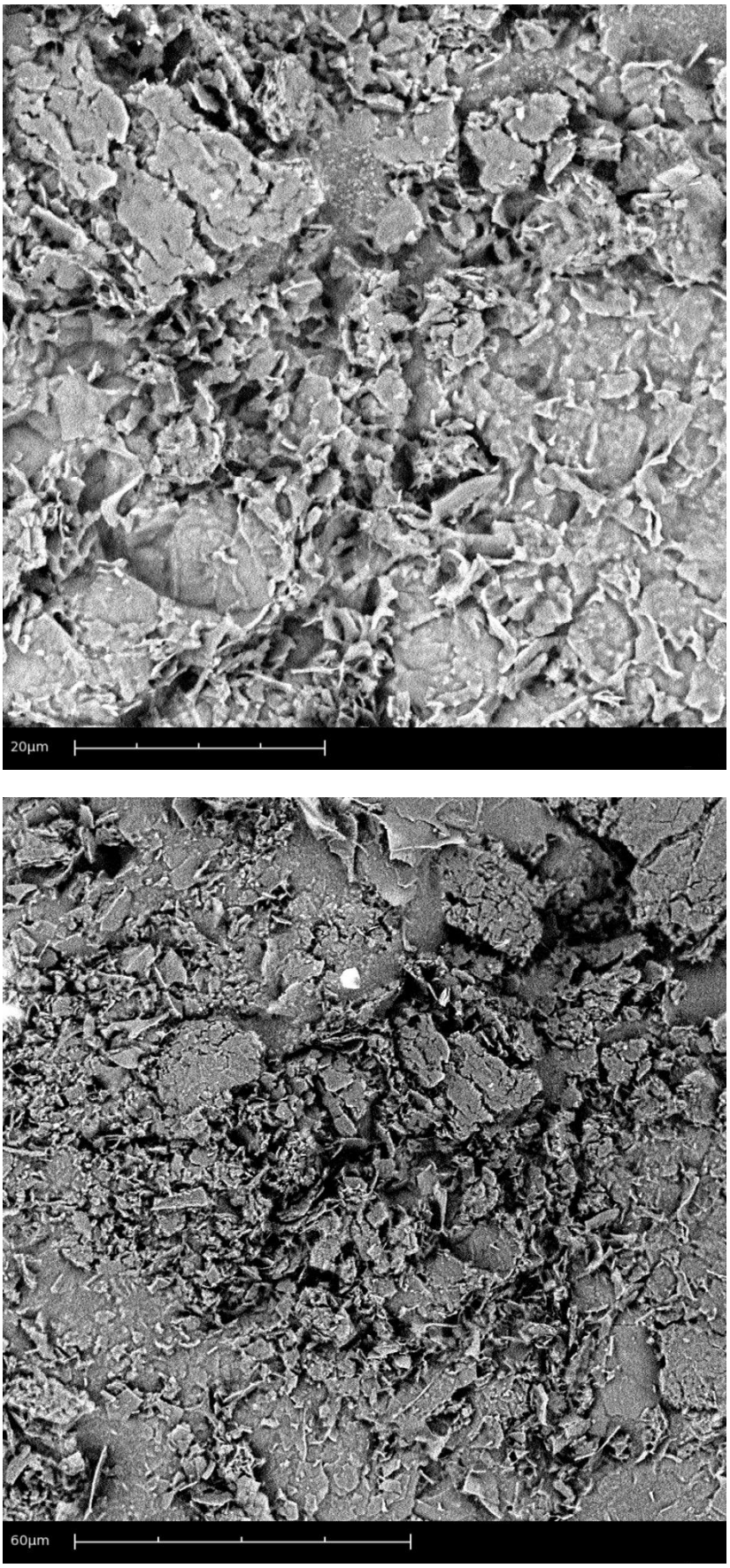


Figure S21. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and phenylalanine (1 equiv.).

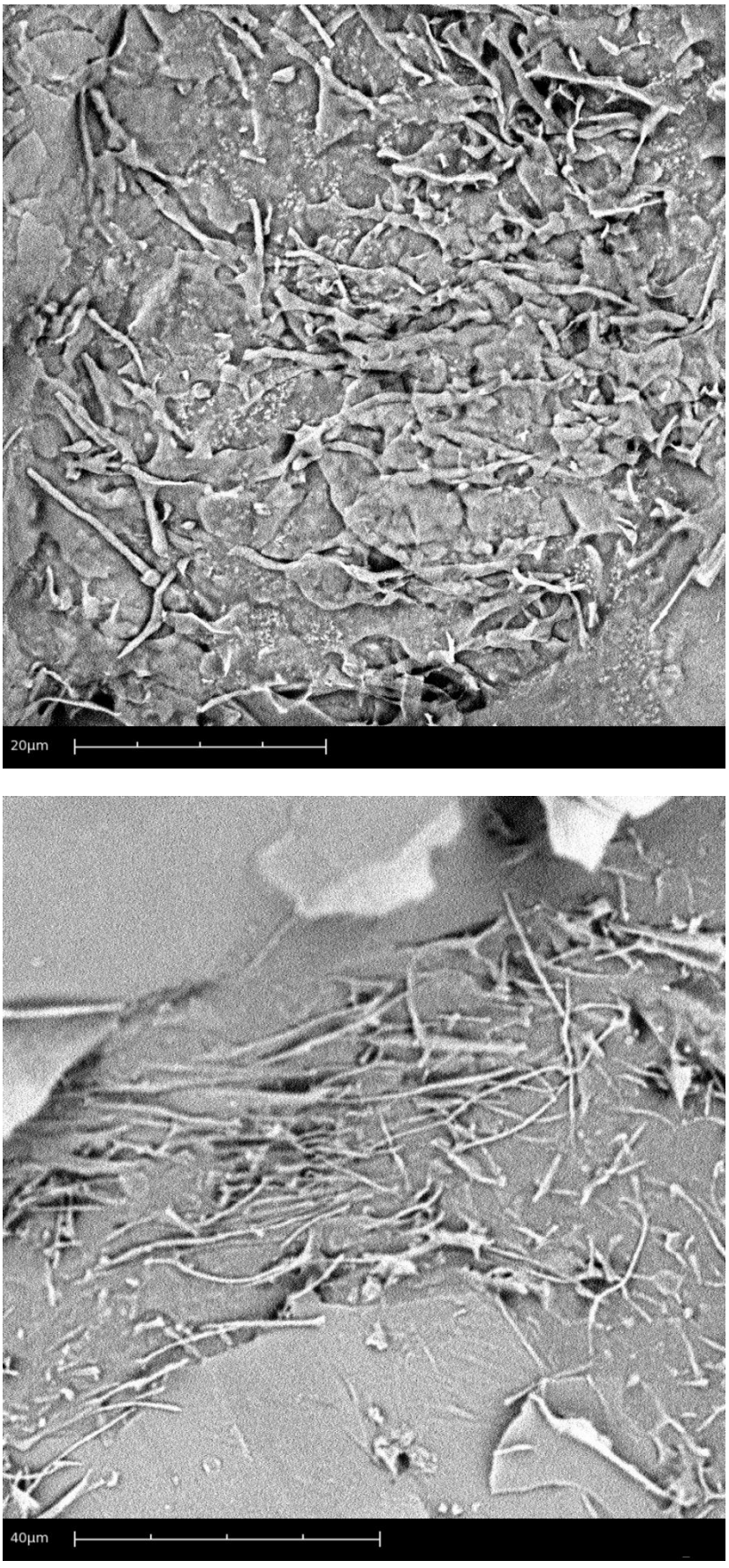


Figure S22. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and phenylalanine (2 equiv.).

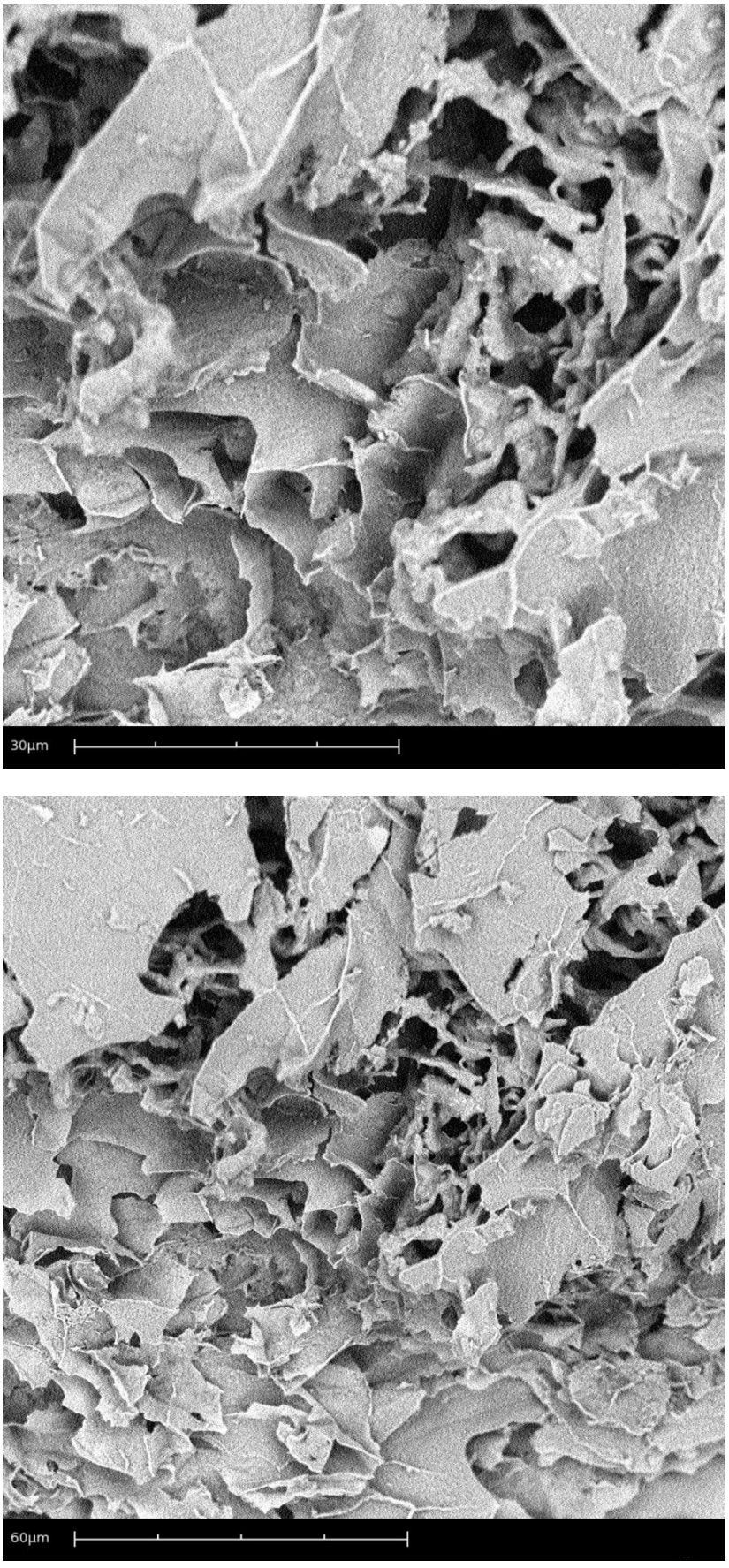


Figure S23. SEM images of a sample of xerogel obtained by freeze drying a sample of hydrogel prepared with **A** in 2% w/w concentration and GdL (2 equiv.).

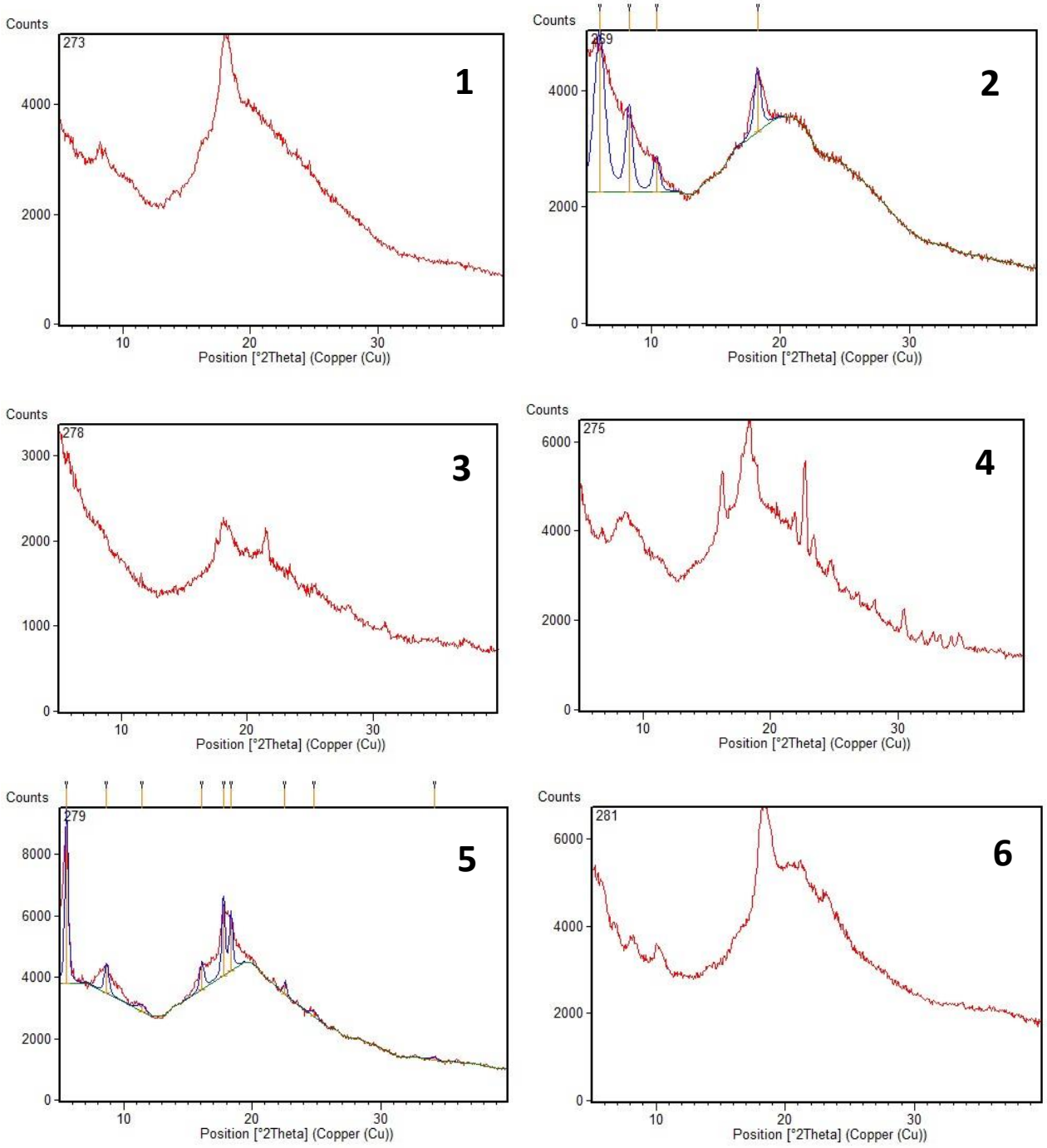


Figure S24. XRD patterns of aerogels prepared by freeze-drying samples of hydrogels **1**-**6**.

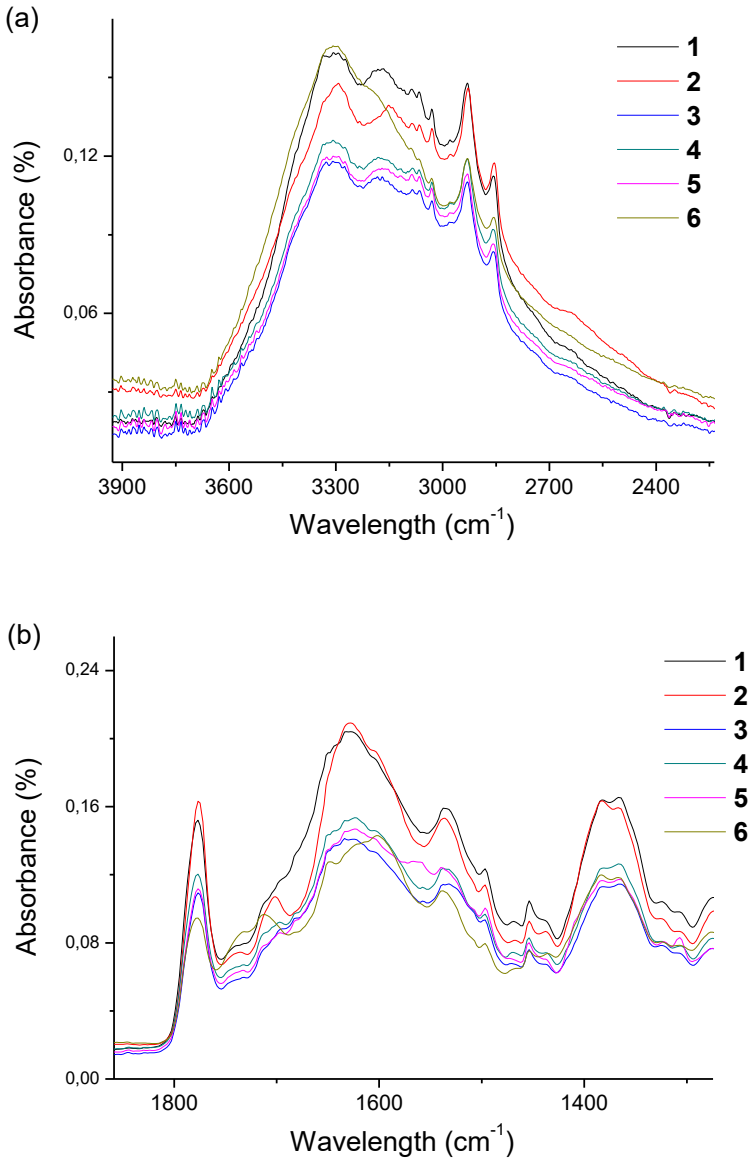


Figure S25. (a) N-H and (b) C=O stretching regions of the IR absorption spectra of aerogels prepared by freeze-drying samples of hydrogels **1**-**6**.

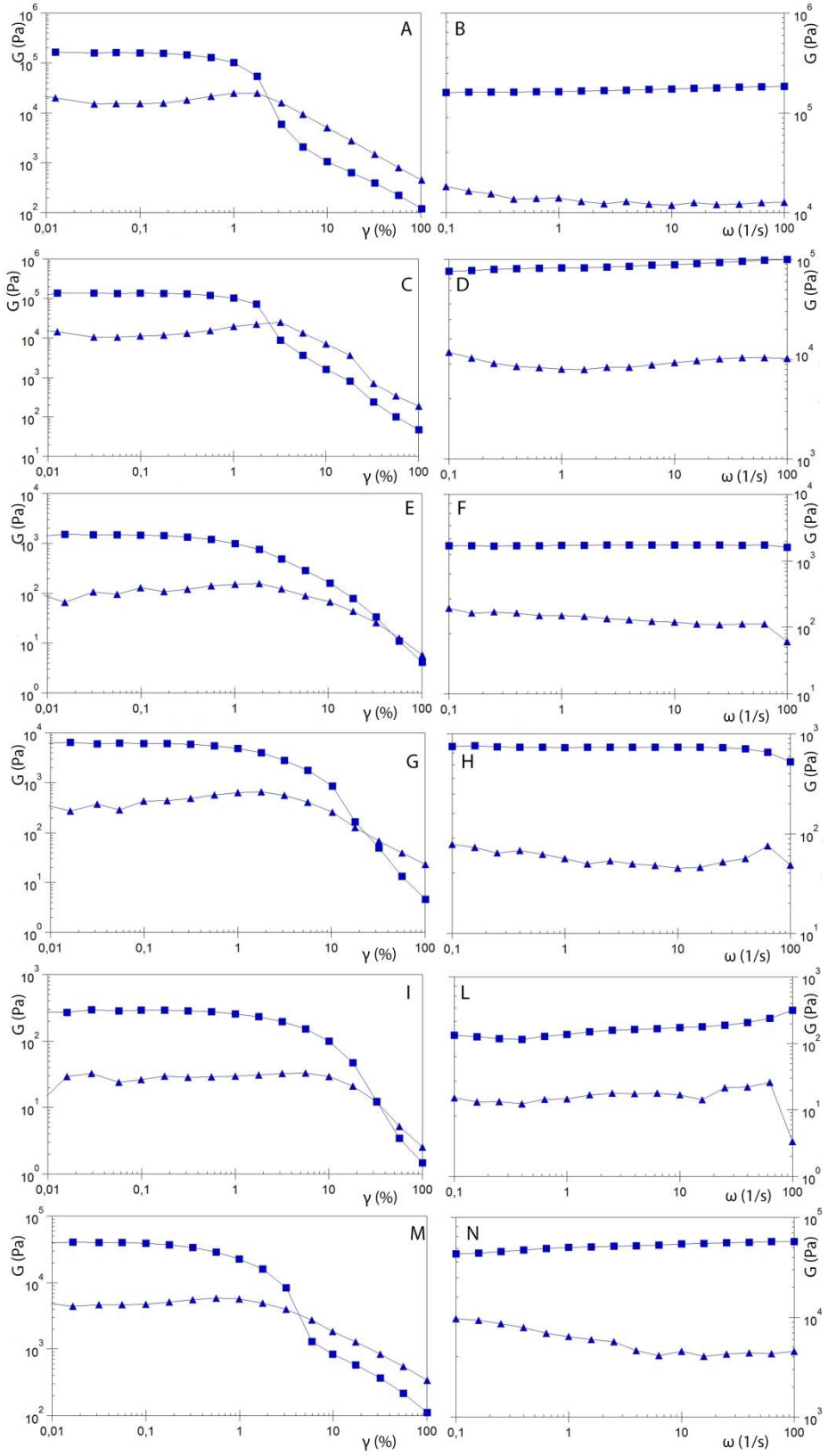


Figure S26. Strain dependence (A-C-E-G-I-M) and frequency dependence (B-D-F-H-L-N) of storage modulus (square) and loss modulus (triangle) for hydrogels **1** (A-B), **2** (C-D), **3** (E-F), **4** (G-H), **5** (I-L), **6** (M-N) .The analyses were performed on the hydrogel about 20 hours after the gelation begun.