Injectable and glucose-responsive hydrogels based on boronic acid–glucose complexation

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General Procedures of Polymer Synthesis

A heating block which can hold 20 ml vials was preheated to 65^{o}C. 20 ml of glass vials with septa were used in multi reactions set up. 3-(Acrylamino)phenylboronic acid (**A**) and tert-butyl (3-acrylamidopropyl)carbamate (**B**) in a desired ratio were dissolved in MeOH (3.5 ml) at rt with stirring. Nitrogen was purged in solution for 30 minutes. 12.5% of 2,2'-Azobis(2-methylpropionitrile) (It was recrystallized before using) was added. The solution was continuously degassed for an additional 30 minutes, heated at 65^{o}C with stirring for one day, then cooled to rt. It was dropwise added to a 200 ml Et_2O. The precipitate was filtered by suction, washed with Et_2O (3x50 ml), dried to get a white solid. Yield: 100% of **A**, 86%; 90:10% of **A**/**B**, 82%; 80:20% of **A**/**B**, 92%; 70:30% of **A**/**B**, 91%; 60:40% of **A**/**B**, 90%; 50:50% of **A**/**B**, 84%; 40:60% of **A**/**B**, 80%; 30:70% of **A**/**B**, 87%; 20:80% of **A**/**B**, 68%; 10:90% of **A**/**B**, 62%; 100% of **B**, 78%. Molecular weight of polymer C was calculated from gel permeation chromatography (GPC; Mn~33K, Mw~54K)

General Procedures of De-protection

To a polymer (~200 mg) were added dichloromethane (6 ml) followed by TFA (3 ml). The suspension was stirred at rt for one day. The solvents were evaporated on rotavap. Methanol was added to dissolve oily residue and evaporated subsequently. This procedure was repeated for three times to get rid of excess TFA as much as possible to leave a white solid, which was dried further under high vacuum pump overnight.

General Procedures of Reductive Amination

A mixture of de-protected polymer, glucose and sodium triacetoxyborohydride in DMF (3 ml) and THF (6 ml) was stirred at rt for one day. The amount of glucose (1 equiv.) and sodium triacetoxyborohydride (1.2 equiv.) depended on amount of **B** in polymer synthesis. Majority solvents were evaporated. The residue was dissolved in ultra-pure water (~20 ml), dialyzed (MWCO 1,000) and lyophilized to have a white solid.

Polymer structure characterization by ^{1}HNMR

BC1, 100: 0 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.06-6.82 (m, 5H), 2.69-1.34 (m, 3H).

BC2, 90:10 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.02-6.86 (m, 5H), 3.23-1.27 (m, 6H).

BC3, 80:20 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 7.99-6.94 (m, 5H), 3.23-1.27 (m, 8H).

BC4, 70:30 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.05-6.91 (m, 5H), 3.27-1.26 (m, 15H).

BC5, 60:40 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.03-6.94 (m, 5H), 3.27-1.25 (m, 16H).

BC6, 50:50 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.03-6.93 (m, 5H), 3.27-1.20 (m, 19H).

BC7, 40:60 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.12-7.00 (m, 5H), 3.28-1.26 (m, 25H).

BC8, 30:70 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.03-7.04 (m, 5H), 3.25-1.23 (m, 36H).

BC9, 20:80 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.06-7.14 (m, 5H), 3.28-1.24 (m, 49H).

BC10, 10:90 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 8.03-7.11 (m, 5H), 3.29-1.33 (m, 95H).

BC11, 0:100 of PBA:RNHBoc

^{1}HNMR (500 MHz, CD3OD): δ 3.28-3.14 (m, 2H), 3.14-3.01 (m, 2H), 2.40-1.52 (m, 5H), 1.45 (s, 9H).

BC-NH_2-2, 90:10 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, D_2O): δ 7.98-6.52 (m, 5H), 3.54-0.74 (m, 4H).

BC-NH_2-3, 80:20 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, D_2O): δ 7.83-6.50 (m, 5H), 3.50-0.75 (m, 7H).

BC-NH_2-4, 70:30 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, D_2O): δ 7.50-6.50 (m, 5H), 3.30-1.10 (m, 8H).

BC-NH_2-5, 60:40 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, CD_3OD): δ 7.72-6.81 (m, 5H), 3.42-1.12 (m, 9H).

BC-NH_2-6, 50:50 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, CD_3OD): δ 7.87-6.94 (m, 5H), 3.28-1.37 (m, 14H).

BC-NH_2-7, 40:60 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, D_2O): δ 7.77-6.78(m, 5H), 3.41-1.24 (m, 19H).

BC-NH_2-8, 30:70 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, D_2O): δ 7.85-6.91 (m, 5H), 3.43-1.24 (m, 29H).

BC-NH_2-9, 20:80 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, D_2O): δ 8.01-6.90 (m, 5H), 3.25-1.28 (m, 40H).

BC-NH_2-10, 10:90 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, D_2O): δ 7.93-7.11 (m, 5H), 3.38-1.24 (m, 82H).

BC-NH_2-11, 0:100 of PBA:RNH_2.TFA

^{1}HNMR (500 MHz, D_2O): δ 3.37-3.08 (m, 2H), 3.03-2.92 (m, 2H), 2.26-1.30 (m, 5H).

Table 1. State of polymer BG in 5% water

Polymer BG	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
% Monomer B	100	90	80	70	60	50	40	30	20	10	0
% Monomer C	0	10	20	30	40	50	60	70	80	90	100
5% in water	solid	solid	solid	liquid	**gel**	**gel**	**gel**	**gel**	**gel**	**gel**	liquid

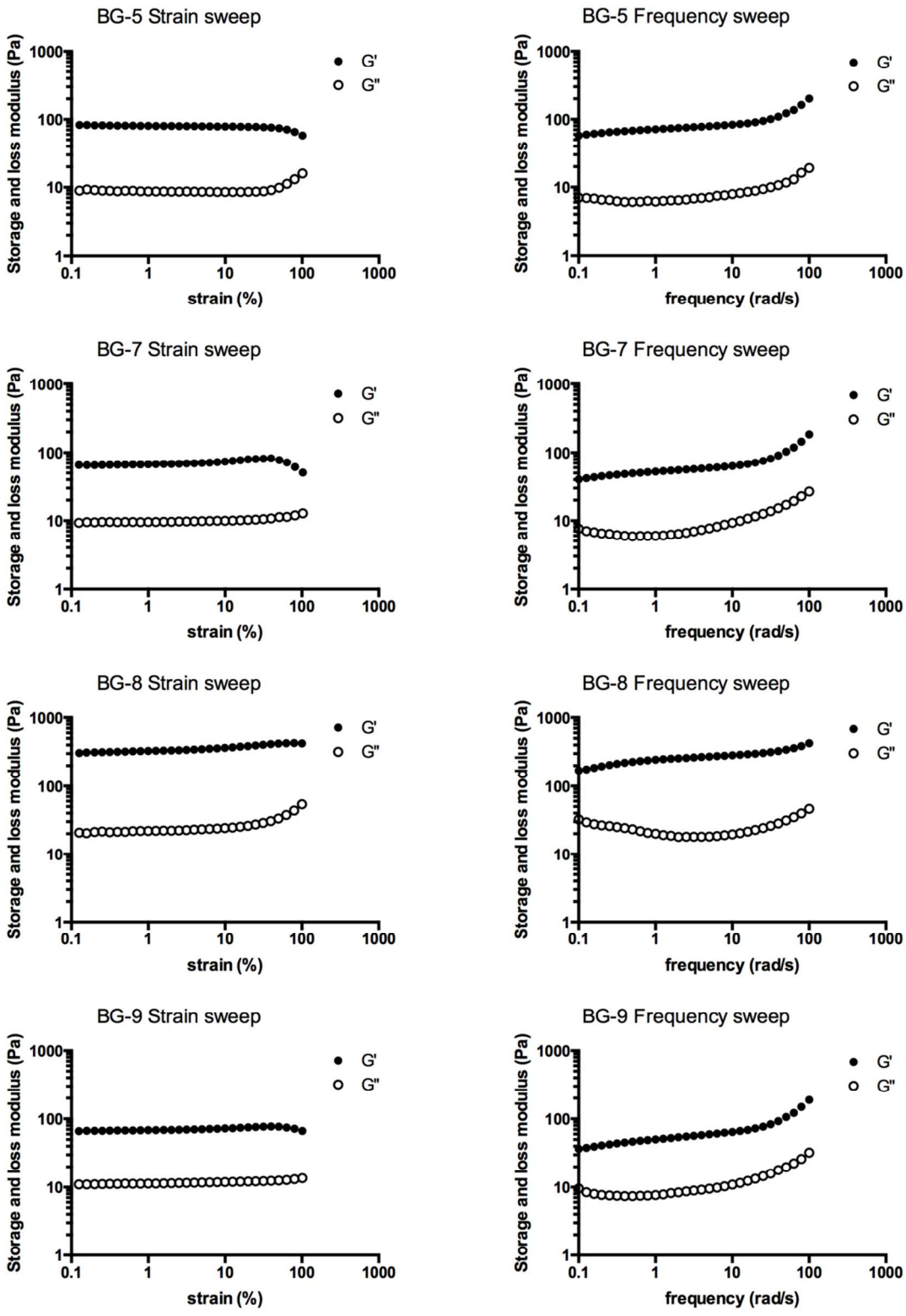

Figure 1. Strain dependence (ω = 10 rad/s) of the storage and loss moduli of BG5, 7, 8, and 9. Frequency dependence (ε = 2%) of the storage and loss moduli of BG5, 7, 8, and 9.

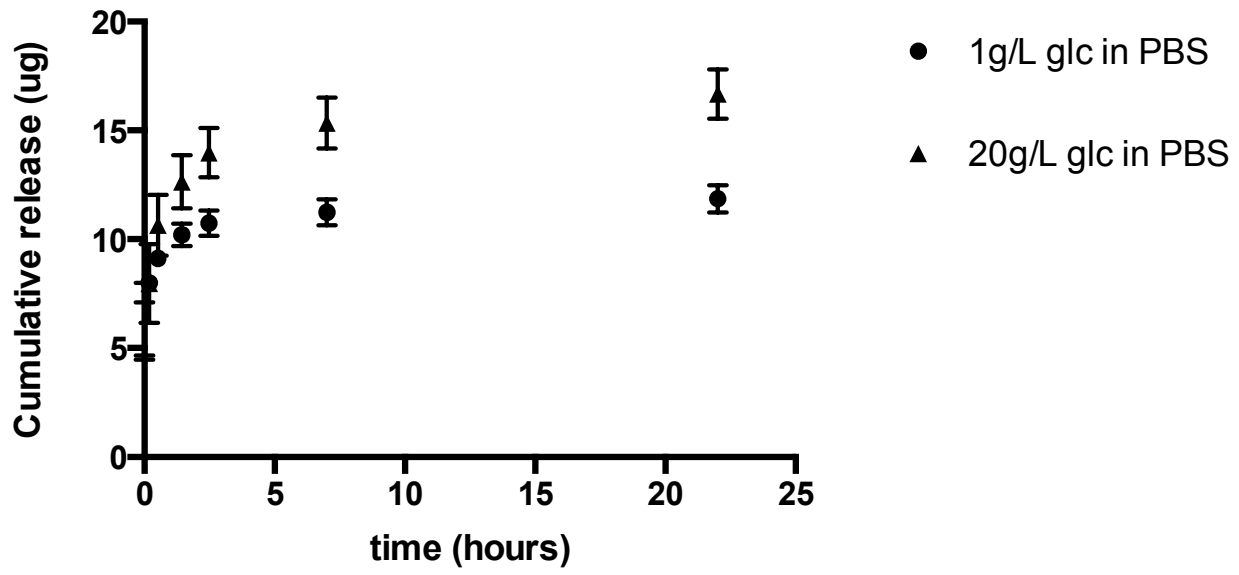

Figure 2. Glucose responsiveness of BG 5. BG 5 released a significantly higher amount of Rhodamine B in a 20 g/L solution compared with that in a 1 g/L glucose solution.