Supporting Information

of

Appointed exploding microcapsules as drug carriers

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Materials

Propargyl alcohol (PA-OH), dextran (M_w~20 k & 200 kDa), 1, 1'-carbonyldiimidazole (CDI), 3-chloropanol, sodium azide (NaN_3), dimethyl sulfoxide (DMSO), sodium ascrobate, polyethylene glycol (20kDa), copper sulfate ($CuSO_4$), magnesium sulfate, sodium sulfate, ether, ethyl acetate, dichloromethane, cystamine dihydrochloride, sodium hydroxide, isopropanol, chloroacetic acid, methanol, hydrochloric acid, Triethylamine (TEA), 1-ethyl-3-3-dimethylaminopropyl carbodiimide (EDC), Rhodamine B, DL-Dithiothreitol (DTT), sodium hydroxide (NaOH), methanol, potassium bromide (KBr) were purchased from Shanghai Reagent Chemical Co. (China). Fluoresceinamine isomer (FITC) was purchased from Acros. Tetrabutylammonium hydrogen sulfate was purchased from Aladdin. All other chemicals were obtained from Shanghai Reagent Chemical Co. (China) and used as received.

Synthesis of 3-azidopropanol

3-azidopropanol was synthesized according to literature.[1] sodium azide (7.83g; 119 mol) and tetrabutylammoniumhydrogen sulfate (0.167g) were dissolved in 20 ml water and 3-Chloropropanol (5ml; 5.66 g; 59.7 mmol) was added. The mixture was stirred at 80°C for 24h and then stirring at room temperature overnight. The solution

was extracted with ether (3 × 30 ml). The resulting solution was dried over sodium sulfate. The solvent was removed by rotary evaporation and after purified by vacuum distillation 3-azidopropanol was obtained as a liquid (yield: 95%). ^{1}HNMR recorded on a Mercury VX-300 spectrometer at 300 MHz (Varian, USA) by using $CDCl_3$ as a solvent and TMS as an internal standard: δ (ppm) 1.84 (m, 2H, -CH_2-C*H*$_2$-CH_2-), 3.46 (t, 2H, -C*H*$_2$-N_3), 3.76 (t, 2H, -C*H*$_2$-OH).

Synthesis of 3-azidopropyl carbonylimidazole (AP-CI) (1)

A dry round bottomed flask was charged with 13.77 g (84.93 mmol) CDI and 150 ml ethyl acetate yielding a turbid suspension. Ethyl acetate was used as solvent instead of dichloromethane to avoid the formation of diazomethane which is prone to detonation. 3-azidopropanol (5.72 g, 56.9 mmol) was added dropwise under vigorous stirring while the reaction mixture turned into a clear solution. After 2 h reaction at room temperature, the solution was extracted three times with 150 ml water. The organic layer was dried over magnesium sulfate. After filtering off the magnesium sulfate, the solvent was evaporated by rotary evaporation and 3- azidopropyl carbonylimidazole (AP-CI) was obtained as a liquid. The yield was 55 %. ^{1}HNMR recorded on a Mercury VX-300 spectrometer at 300 MHz (Varian, USA) by using $CDCl_3$ as a solvent and TMS as an internal standard: δ (ppm) 2.08 (m, 2H, -CH_2-C*H*$_2$-CH_2-), 3.50 (t, 2H, N_3-C*H*$_2$-), 4.52 (t, 2H, -CH_2-CH_2-O-), 7.07 (s, 1H, -C=C*H*-N=), 7.42 (s, 1H, N-C*H*=C-), 8.14 (s, 1H, N-C*H*=N-).

Synthesis of propargyl carbonylimidazole (PPA-CI) (2)

8.11 g (50 mmol) CDI and 110 mL dichloromethane were added into a dry round bottomed flask yielding a turbid suspension. Then 1.7 mL propargyl alcohol dissolved

in 20 mL dichloromethane was added dropwise under vigorous stirring to form a homogenous solution. After reaction at room temperature for 1 h, the mixture was extracted three times with 35 mL water. The organic layer was combined and dried over magnesium sulfate. By filtering the magnesium sulfate and evaporating by rotary evaporation, propargyl carbonylimidazole (PPA-CI; 6.57 g; 82% yield) was obtained as powder after dried in vaccum. $_1$H-NMR in $CDCl_3$ recorded with a Bruker AVANCE 500 MHz spectrometer: δ (ppm) 2.64 (s, 1H, *H*C≡C-), 5.01 (s, 2H, HC≡C-C*H*$_2$-O-), 7.09 (s, 1H, -C=C*H*-N=), 7.46 (s, 1H, N-C*H*=C-), 8.11 (s, 1H, N-C*H*=N-).

Synthesis of propargyl cystamine (3)

A round dry flask was charged with 13 g cystamine dihydrochloride (57.75 mmol), 4.62 g sodium hydroxide (115.5 mmol) and 20ml water. After 1 h stirring at room temperature, the mixture was evaporated to remove the water. Then the residue was redissolved in 40 ml dichloromethane. After filtering off the precipitate, the liquid was dried over magnesium sulfate. By filtering the magnesium sulfate and evaporating by rotary evaporation, cystamine (8.74 g; 67% yield) was obtained as yellow oil after dried in vaccum.

4.4 g Cystamine (28.52 mmol) was dissolved in 30 ml dichloromethane.3.47 g PPA-CI dissolved in 20 ml dichloromethane was added dropwise to the flask with a 50 ml dropping funnel. The reaction was carried out under stirring at room temperature for 24 h. After evaporation of the solvent, the residue was treated with NaH_2PO_4 (100 mL, pH 4.2) and extracted with ether (30mL×3) to remove the diprop-2-ynyl 2, 2'-disulfanediylbis (ethane-2,1-diyl) dicarbamate. The aqueous solution was basified with 1 M NaOH to pH 9.0, and extracted with ethyl acetate

(40mL×3). The organic phase was combined and dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a yellow liquid with a yield of 44.2%. ^{1}HNMR recorded on a Mercury VX-300 spectrometer at 300 MHz (Varian, USA) by using $CDCl_3$ as a solvent and TMS as an internal standard: δ (ppm) 2.49 (t, 1H, *H*C≡C-), 2.77 (m, 2H, -S-S-C*H*$_2$-CH$_2$-NH$_2$), 2.79 (m, 2H, -HN-CH$_2$-C*H*$_2$-S-S-), 3.01 (m, 2H, -S-S-CH$_2$-C*H*$_2$-NH$_2$), 3.54 (m, 2H, -HN-C*H*$_2$-CH$_2$-S-S-), 4.69 (s, 2H, HC≡C-C*H*$_2$-O-).

Synthesis of azide modified dextran (dex-N_3) (4)

In a dry round bottomed flask, 1 g dextran (corresponding to 6.167 mmol glucopyranose repeating units) was dissolved in 20 ml anhydrous DMSO. To this mixture 0.593 g (3.03 mmol) AP-CI and two drop of TEA was added. The reaction was stirred overnight at 50°C under nitrogen atmosphere. Subsequently the reaction mixture was purified by dialysis in dialysis tube (MWCO: 3500) and lyophilized for 5 days. After lyophilisation, dex-N_3 was obtained as white fluffy powder. ^{1}HNMR recorded on a Mercury VX-300 spectrometer at 300 MHz (Varian, USA) by using D_2O as a solvent and TMS as an internal standard: δ (ppm) 1.93 (2H, -CH$_2$-C*H*$_2$-CH$_2$-), 4.92 (1H, dextran, -O-C*H*(CH-OH)-O), 4.26 (t, 2H, -CH$_2$-C*H*$_2$-O-).

Synthesis of carboxymethyl dextran (CMD) (5)

The synthesis of CMD was according to the literature.[15] Briefly, one gram dextran was added into the mixture of isopropanol (22 mL) and 14.3 M aqueous NaOH solution (4 mL), and the mixture was stirred at room temperature (22 ^{o}C) for 1 h. The chloroacetic acid was added dropwise and the suspension was stirred for 90 min at 60 ^{o}C. The product was cooled to room temperature, the isopropanol was removed and

methanol was added. Then the methanol was removed and the residue was dissolved in 20 mL distilled water, the pH of aqueous solution was adjusted to acidic (pH = 2~3) with 1 M HCl to convert -COONa to -COOH. Subsequently, the solution was purified by dialysis in dialysis tube (MWCO: 3500) and freeze-dried for 1 day. The number of carboxyl group to the anhydroglucose unit of CMD was defined as the degree of substitution (DS) and the DS of CMD was evaluated by ^{1}HNMR. DS=0.81. ^{1}HNMR recorded on a Mercury VX-300 spectrometer at 300 MHz (Varian, USA) by using D_2O as a solvent and TMS as an internal standard: δ (ppm): 4.22 (s, 2H, HOO=C-C*H*$_2$-O-dextran), 4.92 (1H, dextran, -O-C*H*(CH-OH)-O-), 5.13 (1H, dextran, -O-C*H*(CH-O-CH$_2$-C=OOH)-O-).

Synthesis of alkyne modified dextran (dex-C≡C) (6)

In a dry round bottomed flask, 0.667 g (4.13 mmol) CMD was dissolved in 50 ml DMSO/H_2O (v/v=1:1). To this mixture 0.963 g (4.13 mmol) PPA-CI, 0.947 g NHS (8.26 mmol) and 1.577 g (8.26 mmol) EDC were added. The reaction was stirred overnight at 50 ^{o}C for 24 h. Subsequently the reaction mixture was purified by dialysis in dialysis tube (MWCO: 3500) and lyophilized for 5 days. Dex-C≡C was obtained as a white fluffy powder. ^{1}HNMR recorded on a Mercury VX-300 spectrometer at 300 MHz (Varian, USA) by using D_2O as a solvent and TMS as an internal standard: 2.47 (2H, *H*C≡C-CH$_2$), 4.55 (2H, HC≡C-C*H*$_2$), 4.83 (1H, dextran, -O-C*H*(CH-OH)-O), 5.07 (1H, dextran, -O-C*H*(CH-O-CH$_2$-C=OO-)-O).

Fourier Transform-Infrared Spectroscopy

The samples were analyzed by FT-IR (Perkin–Elmer Spectrum One, USA) spectrophotometer. Before the measurements, the samples were pressed into potassium bromide (KBr) pellets.

Fabrication of dextran click microgels.

8.875 mg dex-N_3 and 8.875 mg dex-C≡C were dissolved in 400 µl DI water. This solution was added to 635 µl of 24 % (w/w in pure water) polyethylene glycol solution. The mixture was vortexed for 60 s and then stand still for 15 min. $CuSO_4$ (17 µl of a 50 mg/ml) and sodium ascorbate (17 µl of a 50 mg/ml) were added to initiate click reaction. The reaction was allowed to proceed for 3 h followed by the addition of water (2 ml) and 3 centrifugation (6000 r/min × 2 min)/washing steps with 1 ml water. Finally the obtained microgels were stored in 1 ml water. FITC-dextran was encapsulated in the microgels by the addition of 4 mg dextran-FITC before the emulsification step.

LbL coating of the dextran click microgels.

500 µL (30 mg/ml) microgels were dispersed in 1 ml polyelectrolyte solution (2 mg/ml in DI water at pH 7) and shaked for 15 min. The excess polyelectrolyte was removed by centrifugation at 6000r/min for 2 min. Then the microgels were washed with 1 ml DI water and centrifuged (6000r/min × 2 min) for two times. This procedure was repeated until three polyelectrolyte bilayers were obtained.