Electronic Supplementary Information

Reduction-responsive molecularly imprinted nanogels for drug delivery applications

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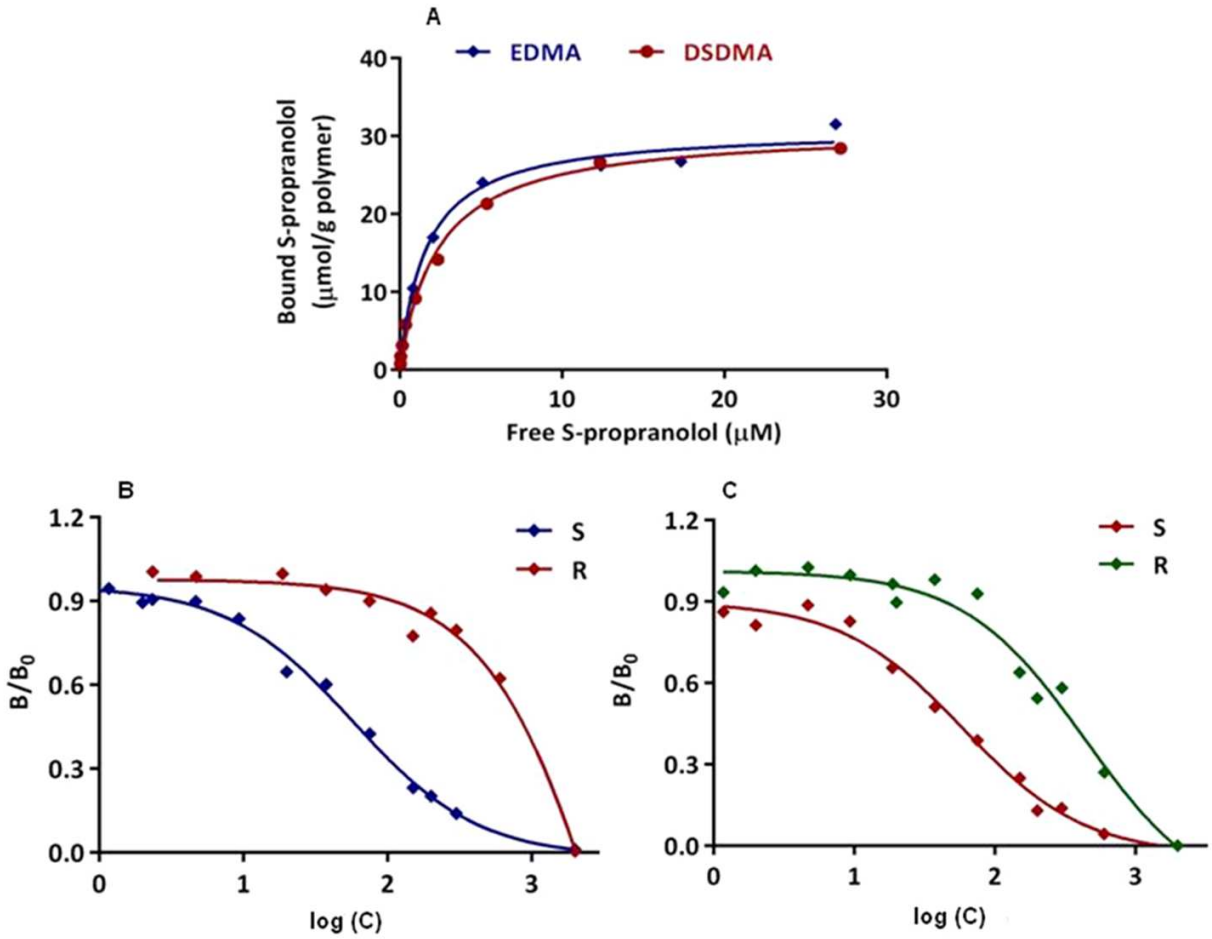

Figure S1: Langmuir isotherms for EDMA-MIP and DSDMA-MIP (A).Displacement of [^{3}H]-*S*-propranolol binding to EDMA (B) or DSDMA (C) cross-linked bulk polymers in acetonitrile by increasing concentrations of competing ligand (*R*-propranolol or *S*-propranolol).

Quantification of disulfide bonds cleavage

Ellman's reagent (DTNB) was used to detect and quantify thiol groups UV-Vis spectrophotometrically.[1] The principle of this test is shown in figure S2. First, disulfide bonds of DSDMA are reduced by $NaBH_4$ to form thiols, which react with Ellman's reagent. A thiol-TNB adduct is formed with a concomitant release of one equivalent of TNB, which is measured spectrophotometrically at 412 nm. DSDMA-MIP or EDMA-MIP concentration was varied from 0 mg/mL to 5 mg/mL, with a fixed amount of DTNB (20 mM). After 10 min reaction, the solution was centrifuged and the absorbance of TNB in the supernatant recorded at 412 nm.

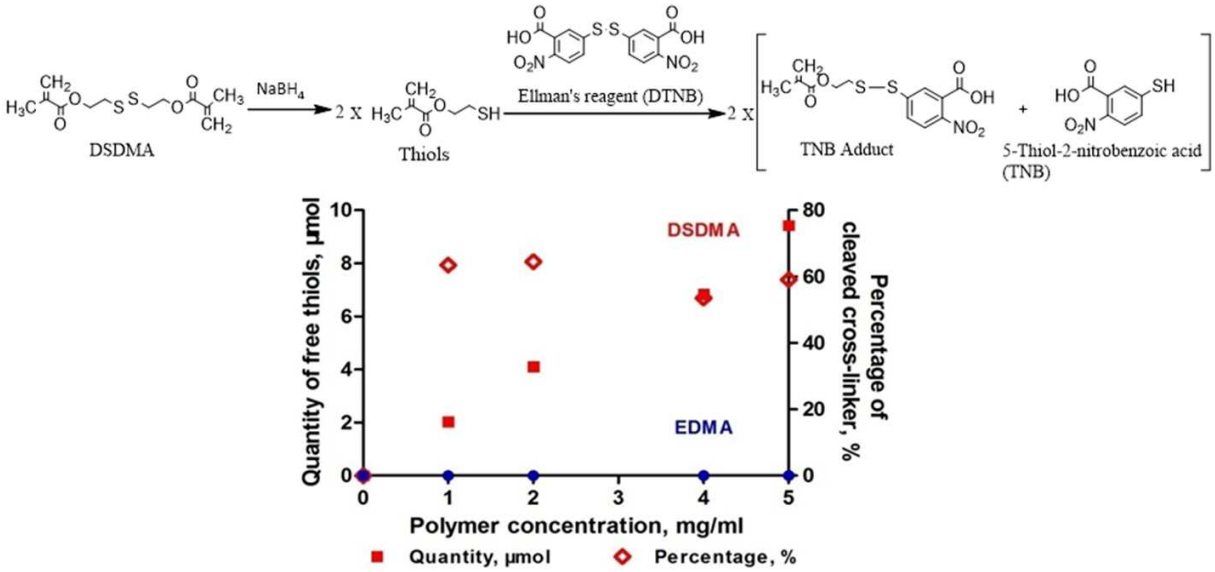

Figure S2: Principle of DSDMA reaction with Ellman's reagent (A), quantity of free thiols released and percentage of cleaved cross-linker for DSDMA-MIP and EDMA-MIP after the incubation with DTNB (B).

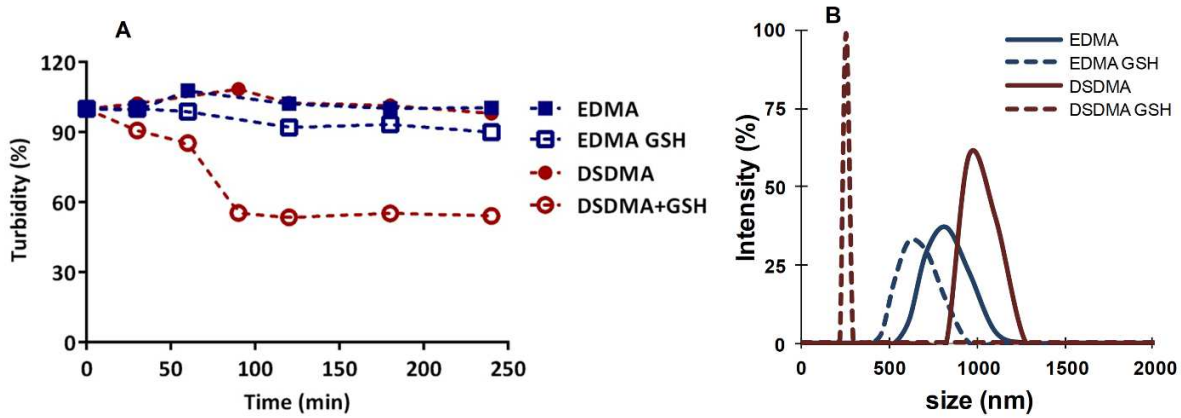

Figure S3: Turbidity evolution (A) and particle size (B) of nanogel (EDMA or DSDMA) solutions (1g/L) in 100 mM sodium acetate buffer pH 5 with or without GSH (10 mM), measured by UV-Vis spectroscopy at 600 nm and DLS, respectively.

Synthesis of fluorescence-tagged nanogels

Cleavable NIP nanogels tagged by the solvochromic dye 8-anilino-1-naphthalenesulfonic acid (ANS) were prepared in the same way as non-tagged NIP nanogels except that ANS (0.033 mmol) was added to the polymerization solution. The hydrodynamic diameter of nanogels was determined by dynamic light scattering at 25 °C using a Zetasizer Nano ZS (ZEN 3600, Malvern Instruments Ltd) with a laser of 4 mW (He-Ne), λ=632 nm, 173°, backscatter.

The cytotoxicity test of DSDMA-based nanogels was performed with human keratinocytes (HaCaT cells) *in vitro* by a standard MTT assay, as previously described.[2]

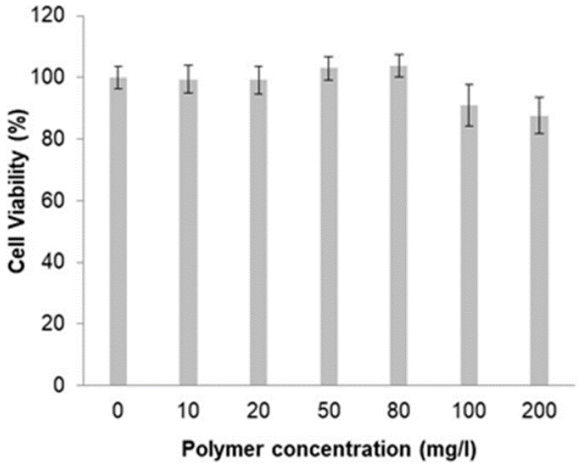

Figure S4: Cell viability test of fluo-tagged nanogels against HaCaT cells after 24 h incubation.

For nanogel degradation by GSH, DSDMA-based nanogel solutions (1 mg/mL) were mixed with GSH (20 mM) in oxygen-free sodium acetate buffer (100 mM, pH 5.0). The quenching of ANS fluorescence due to its release in polar media was monitored by spectrofluorimetry (Fluorolog, HORIBA) with excitation and emission wavelengths, respectively, at 346 nm and ranging from 400 nm to 650 nm. Control experiments were carried out in the same way but without GSH.

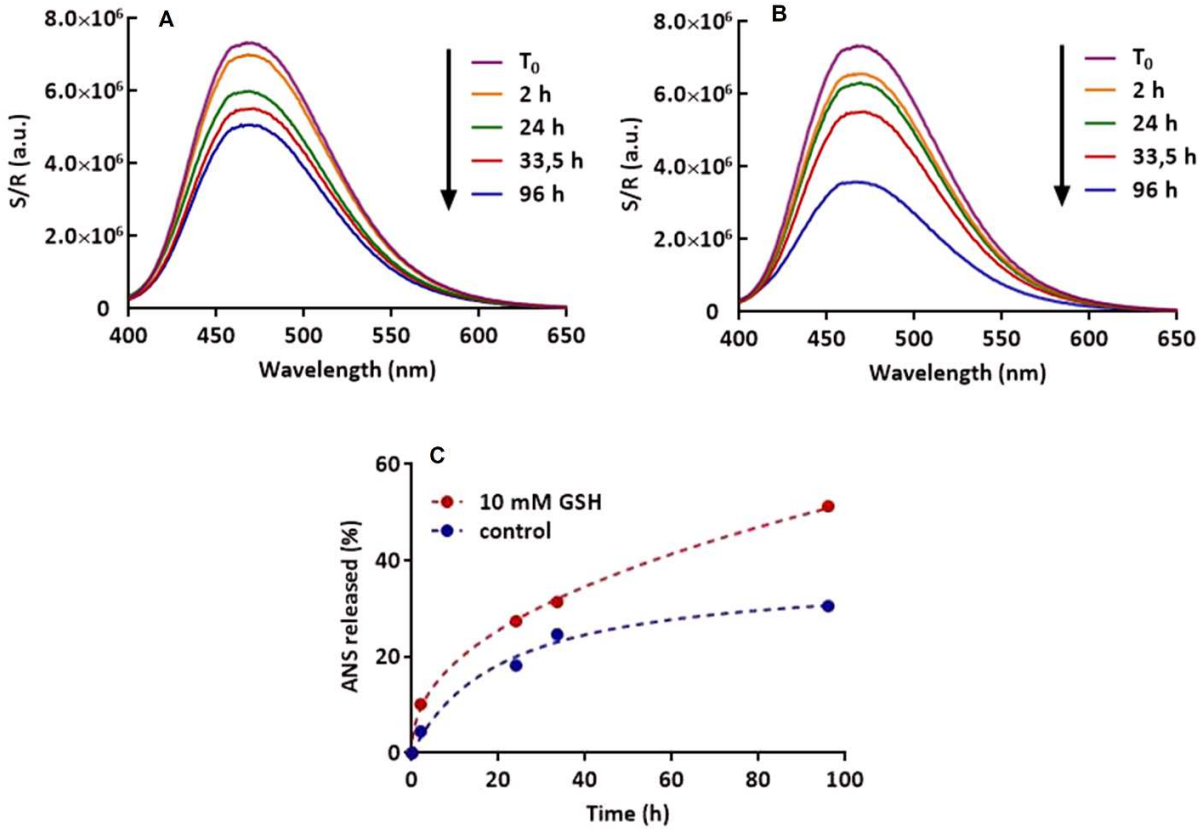

Figure S5: Release of ANS from nanogels with or without presence of GSH. Spectra recorded after preset reaction time of fluo-tagged nanogel cross-linked by DSDMA with (A) or without presence of 10 mM GSH (B) in sodium acetate buffer (0.1 M, pH 5.0) and the resulting ANS kinetic release measured with an emission wavelength at 470 nm (c).

Release kinetics modelling

The *S*-propranolol release kinetics were fitted with the Peppas model (equation 1) to analyze the release mechanism of *S*-propranolol from MIP and NIP nanogels in the presence or not of GSH.[3]

$$\frac{M_t}{M_\infty} = kt^n \text{ (Eq 1)}$$

where M_t/M_∞ are the fraction of *S*-propranolol release, k is the Peppas model constant, t the time and n the release exponent. The release mechanism, defined by the n value and the constant k is determined from the equation 2:

$$\ln\left(\frac{M_t}{M_\infty}\right) = n\ lnt + lnk \text{ (Eq 2)}$$

Table S1: *S*-propanolol release kinetic parameters fitted by the Peppas model.

Release test	**n**	**k**	**R^2**	**mechanism**
NIP	0.44	0.282	0.9769	Fickian
MIP	0.87	0.280	0.8705	Non-Fickian
MIP+ GSH	0.52	0.359	0.9997	Non-Fickian

REFERENCES

1 W. Chen, Y. Zhao, T. Seefeldt and X. Guan, *Journal of pharmaceutical and biomedical analysis*, 2008, **48**, 1375.

2 F. Shi, J. Ding, C. Xiao, X. Zhuang, C. He, L. Chen, X. Chen, *Journal of Materials Chemistry*, 2012, **22**, 14168.

3 G. W. Sinclair and N. A. Peppas, *Journal of Membrane Science,* 1984, **17** (3), 329.