Supplementary data

Biodegradable gemini multiblock poly(ε-caprolactone urethane)s toward controllable micellization

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TP loading into micelles

Triptolide (TP) was loaded into multiblock poly(ε-caprolactone urethane) micelles by a micelle extraction technique.[3-5] Accurately weighted amounts of TP were added to methanol. After complete dissolution, the solvents were evaporated overnight, leaving a thin film of the TP inside. 10 mL of micelle solutions were then transferred to the vials containing TP film and ultrasonated for 1 h. The loaded micelle solutions were centrifugalized at 2500 r/min for 10 min, and passed through a 0.45 μm pore-sized syringe filter (Milipore, Carrigtwohill, Co. Cork, Ireland) to remove the excess TP. The amount of TP loaded inside micelles was analyzed by UV-vis spectrometer (UV-1800PCS, Mapada Instruments), using the UV-vis absorption calibration curves generated from the TP standard solutions at known concentrations in methanol/water at 90/10% (v/v). The loading content (%) and encapsulation efficiency (%) of the polyurethane micelles were calculated based on the equations below

Loading content (LC) (%) = mass of TP in micelles / total mass of loaded micelles × 100%

Encapsulation efficiency (EE) (%) = mass of TP in micelles / initial amount of feeding TP × 100%.

Turbidity measurements

The optical turbidity of the micellar solutions was measured by using a UV-vis spectrometer (UV-1800PCS, Mapada Instruments). The absorbance of each sample was recorded at 650 nm and collected at ambient temperature. Each measurement was performed in triplicate.

Supplementary discussion

Triptolide (TP) was chosen as the model hydrophobic drug. It is a diterpene triepoxide, the principal active ingredient in extracts from the Chinese medicinal herb *Tripterygium wilfordii* Hook. f, which belongs to the Celastraceae family of plants.[6,7] Recently, TP was shown to possess extensive pharmacological activities including immunosuppression,[8,9] anti-inflammatory[10,11] and antitumor properties.[12,13] However, the clinical use of TP is limited by its poor water solubility and some side effects. Thus a variety of drug delivery systems such as polymeric micelles have been widely developed to deliver TP to reduce its toxicities.[9,14] In our work, the encapsulation of TP by the novel multiblock poly(ε-caprolactone urethane) micelles were studied to verify the

qualification of these polyurethanes as hydrophobic drug carriers. The TP loading in micelles was determined by varying the feed weight ratio of drug to the multiblock polyurethanes. Fig. S5 shows the amount of TP loaded into G30PUEOm20 micelles at various feed weight ratios. One can see that the polyurethane micelles displayed a strong capacity for drug encapsulation, with high TP loading content and encapsulation efficiency of 24% and 94% being obtained, respectively, which are much higher than those for the conventional linear amphiphilic block copolymer micelles.[9] As has been suggested previously, self-assemblies based on amphiphilic copolymers with nonlinear structures exhibit higher encapsulation efficiency.[15,16] In this study, the enhanced drug encapsulation is attributed to the unique nonlinear structure of the multiblock poly(ε-caprolactone urethane)s as well as extraordinary surfactant features provided by gemini groups. In addition, the drug loading content was found to increase with the ratio of drug to polyurethane (Fig. S5). However, the encapsulation efficiency decreased when the initial weight ratio of TP to polyurethane exceeded 1:10. This is because the hydrophobic interaction between drug molecules was greater than that between drug and poly(ε-caprolactone urethane)s due to the high lipophilic character of TP as the drug amount increased, thus the aggregation of saturated and unloaded TP would occur during the loading process.[17]

It is known that the drug-solubilized polymer micelles in aqueous solution tend to become unstable as the drug loading content increases, which is generally caused by the enhanced hydrophobicity of micelles after loading of poorly soluble drugs.[18] In this study, to evaluate the stability of TP-loaded polyurethane micelles, drug concentration-dependent variance in turbidity of micellar solutions was determined by UV-vis spectrometer,[19] the results are shown in Fig. S2. As can be seen, no remarkable change in micelle sizes and turbidity was observed at varying drug feed concentrations, thus suggesting that these polyurethane micelles have a good physical stability even at a high TP loading without formation of TP precipitates or secondary aggregates between micelles.[18] This results were fully supported by DLS and TEM studies (Fig. S6), where the micelle size increased slightly after loading TP, owning to the reduced amount of unimolecular micelles and increase of micellar associates, as can be seen obviously from Fig. S6. Most of the drug free and drug loaded micelles have number-average diameters less than 50 nm, with well defined spherical morphology confirmed by TEM observation. Furthermore, it is noteworthy that the drug loaded micelles have a relatively narrower size distribution and more regular shape compared with empty micelles.

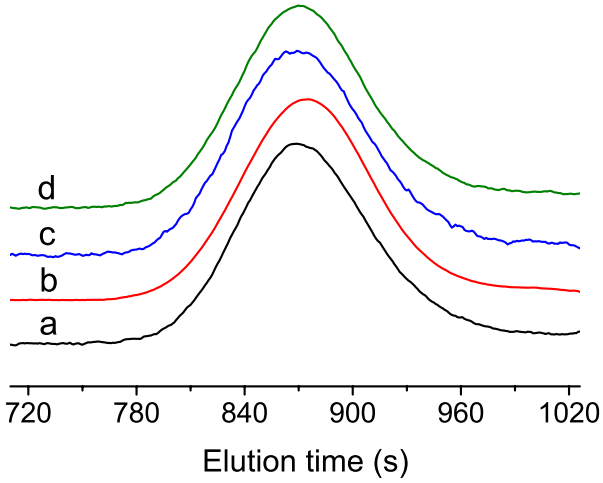

Fig. S1 GPC diagrams of poly(ε-caprolactone urethane)s:

(a) G30PUEOm0, (b) G30PUEOm5, (c) G30PUEOm10 and (d) G30PUEOm20.

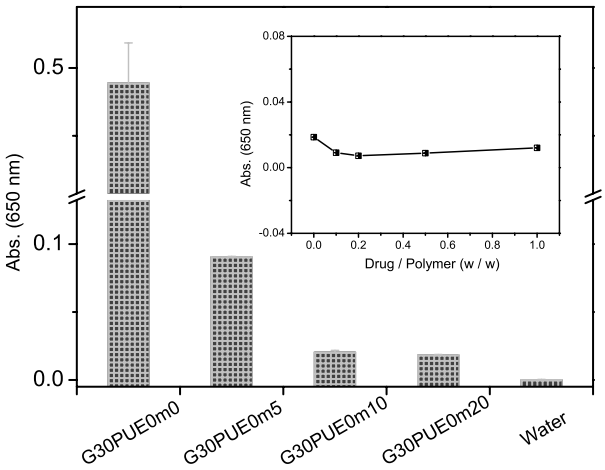

Fig. S2 Turbidity measurements of micellar solutions prepared from different polyurethanes at 1 mg/mL, and TP-loaded micelles of G30PUEOm20 with varying drug feed ratios (inset).

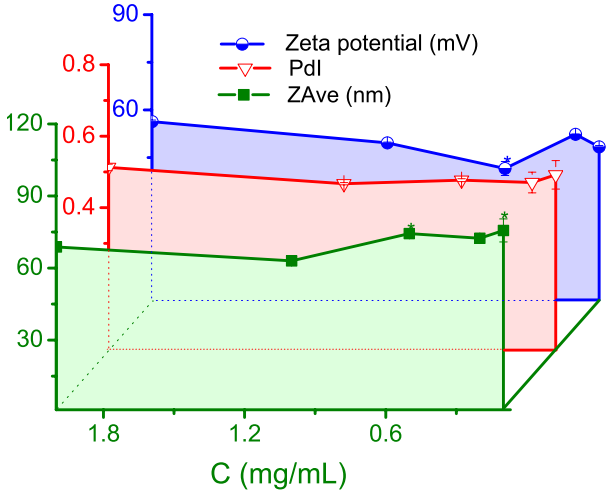

Fig. S3 Dependencies of Size, PdI and zeta potential (ZP) as a function of micelle concentration of G30PUEOm10.

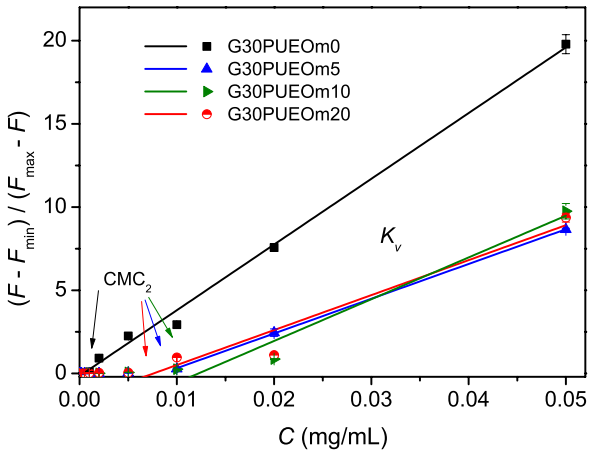

Fig. S4 Plot of $(F - F_{min})/(F_{max} - F)$ *vs.* polyruethane micelle concentrations.

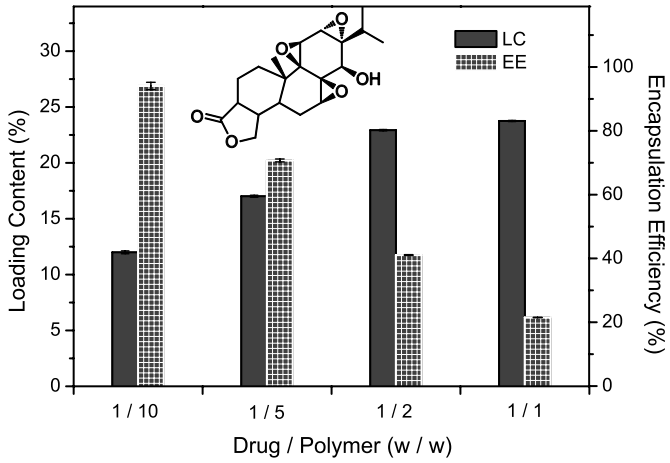

Fig. S5 Drug loading content and encapsulation efficiency of micelles prepared from G30PUEOm20. The inset shows the chemical structure of TP.

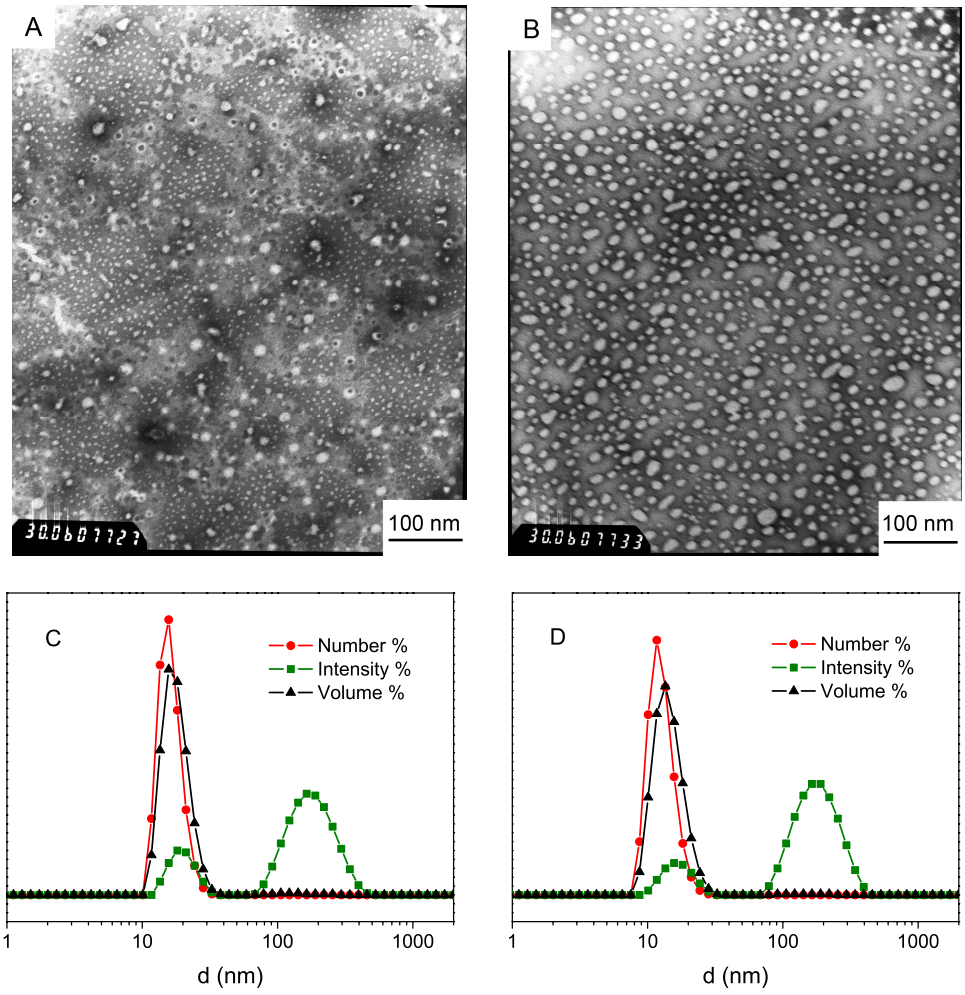

Fig. S6 Typical TEM micrographs (A, B), size and size distribution curves (C, D) of multiblock polyurethane micelles before (left) and after (right) loading of TP.