Supporting information

Crosslinked casein-based micelles as a dually responsive drug delivery system

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Crosslinking mechanism between CAS amino groups and GAL

**Figure S1.** Simplified probable crosslinking mechanism of amino side chains of proteins with GAL.

The remaining amino groups after the crosslinking reaction were determined on the basis of the measured absorbance and a calibration curve (Fig. S3), which was related to the absorbance (at 340 nm) with the amino concentration obtained with glycine as the standard. Thus, the number of initial amino groups/CAS molecule was calculated as follows:

$$N^\circ NH_2 /CAS\ molecule = \frac{A_{CAS}}{a} \times f \times k$$

Where $A_{CAS}$ is the casein absorbance, $a$ is the slope of the calibration curve, $f$ is the dilution factor of the sample, and $k$ is a conversion constant from mM concentration to number of amino groups/CAS molecule, which included the sample volume (100 µL) and the average molecular weight of casein (30 kDa).
Figure S2. Calibration curve from glycine standard used for the calculation of remaining amine groups by the OPA method after the crosslinking process.

Figure S3. Mixture of reaction CCM$_{14}$ before (left) and after (right) the crosslinking process showing a change in the color dispersion.
Structural stability of CCM\textsubscript{14} against 0.01 M NaOH (pH 12) and citrate

**Figure S4.** Size distribution by intensity of CCM\textsubscript{14} and non-crosslinked micelles, after addition of 0.01 M NaOH (a) and sodium citrate (b) as dissociating agents.
Enzymatic degradation of CCM$_{14}$ over time

Figure S5. Hydrodynamic diameter of CCM$_{14}$ during the incubation at 37 °C for 24 h in buffer of pH 5 containing trypsin.

Videos

https://drive.google.com/open?id=1RCyfh_i90qAcUSLfoYdnu0EVuy2Scxrj5