

## Supporting information

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

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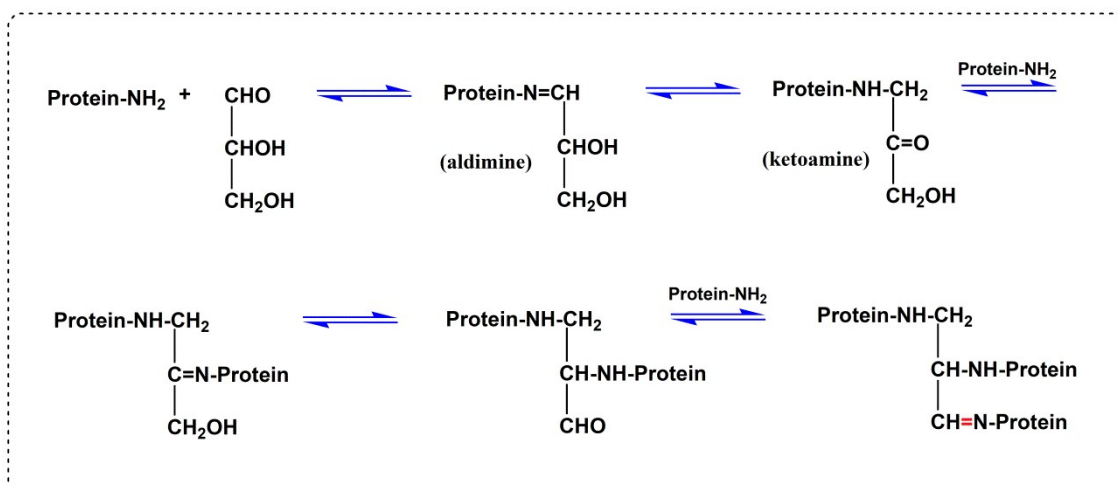
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## Crosslinking mechanism between CAS amino groups and GAL

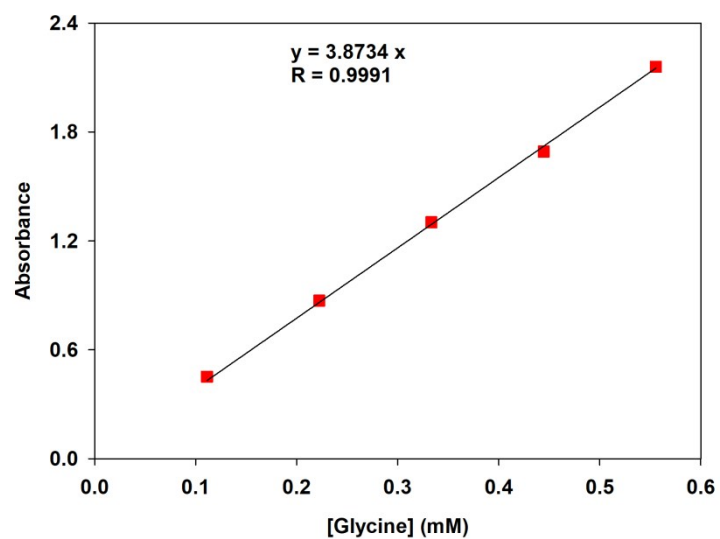


**Figure S1.** Simplified probable crosslinking mechanism of amino side chains of proteins with GAL.

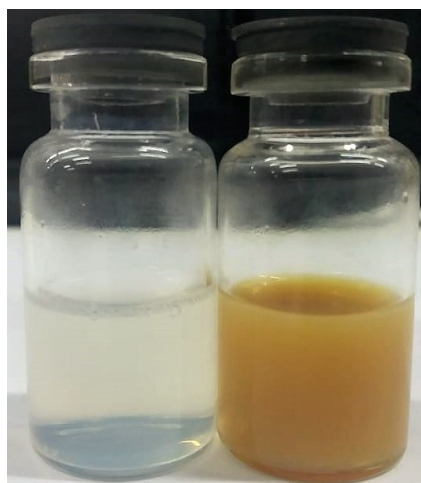
The remaining amino groups after the crosslinking reaction were determined on the basis of the measured absorbance and a calibration curve (Fig. S3), which was related to the absorbance (at 340 nm) with the amino concentration obtained with glycine as the standard. Thus, the number of initial amino groups/CAS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

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

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  $\mu$ L) and the average molecular weight of casein (30 kDa).

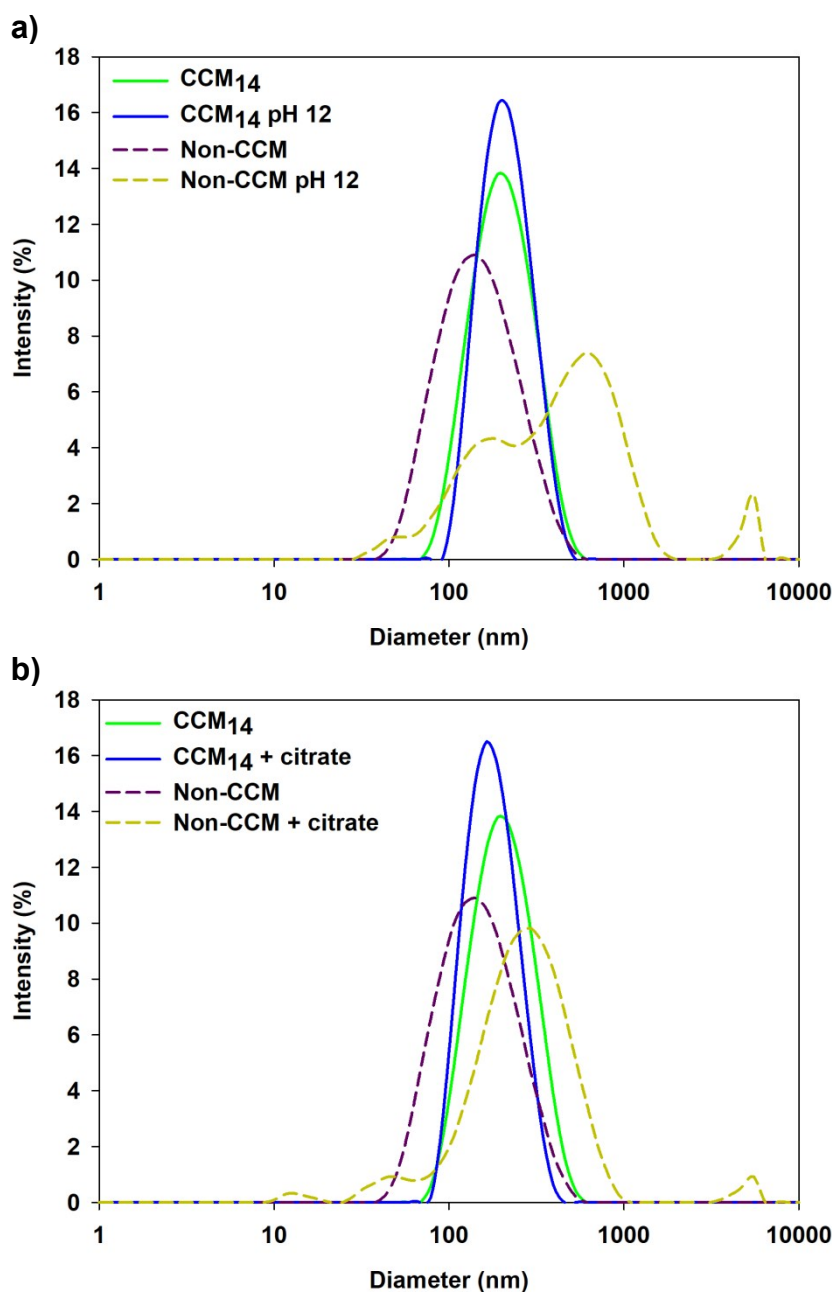


**Figure S2.** Calibration curve from glycine standard used for the calculation of remaining amine groups by the OPA method after the crosslinking process.



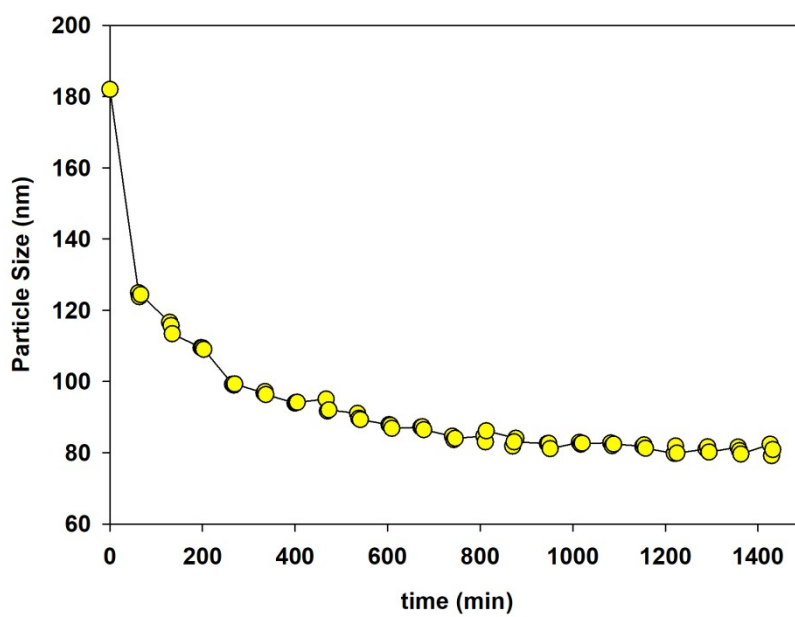
**Figure S3.** Mixture of reaction  $CCM_{14}$  before (left) and after (right) the crosslinking process showing a change in the color dispersion.

### Structural stability of CCM<sub>14</sub> against 0.01 M NaOH (pH 12) and citrate



**Figure S4.** Size distribution by intensity of CCM<sub>14</sub> and non-crosslinked micelles, after addition of 0.01 M NaOH (a) and sodium citrate (b) as dissociating agents.

## Enzymatic degradation of CCM<sub>14</sub> over time



**Figure S5.** Hydrodynamic diameter of CCM<sub>14</sub> during the incubation at 37 °C for 24 h in buffer of pH 5 containing trypsin.

## Videos

[https://drive.google.com/open?id=1RCyfh\\_i90qAcU5LfoYdn0EVuy2Scxrj5](https://drive.google.com/open?id=1RCyfh_i90qAcU5LfoYdn0EVuy2Scxrj5)