Electronic Supplementary Information for

Novel cyanoacrylate-based matrix excipient in HPMCP capsule forms a sustained intestinal drug delivery system for orally administered drugs with enhanced absorption efficiency

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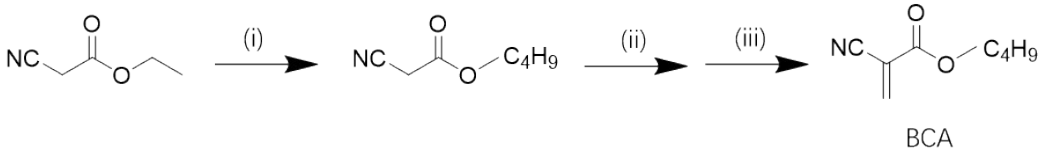
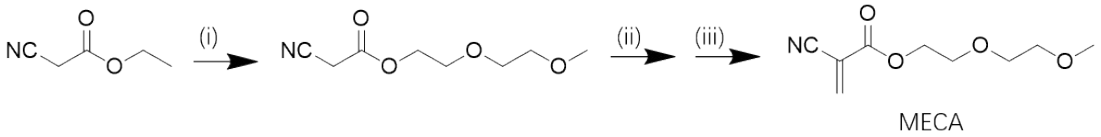
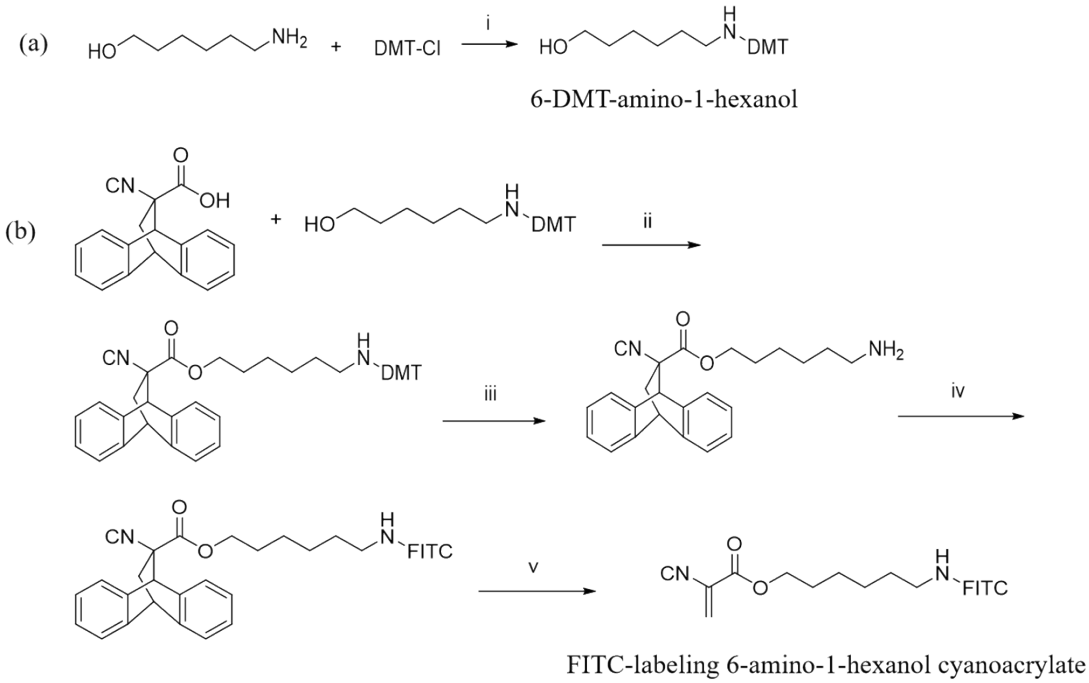


Scheme S1. Synthesis of n-butyl cyanoacrylate (BCA). (i) N-butyl alcohol, tetrabutyl titanate, 3 h reflux. (ii) Formaldehyde, 3 h reflux. (iii) Pyrolysis.



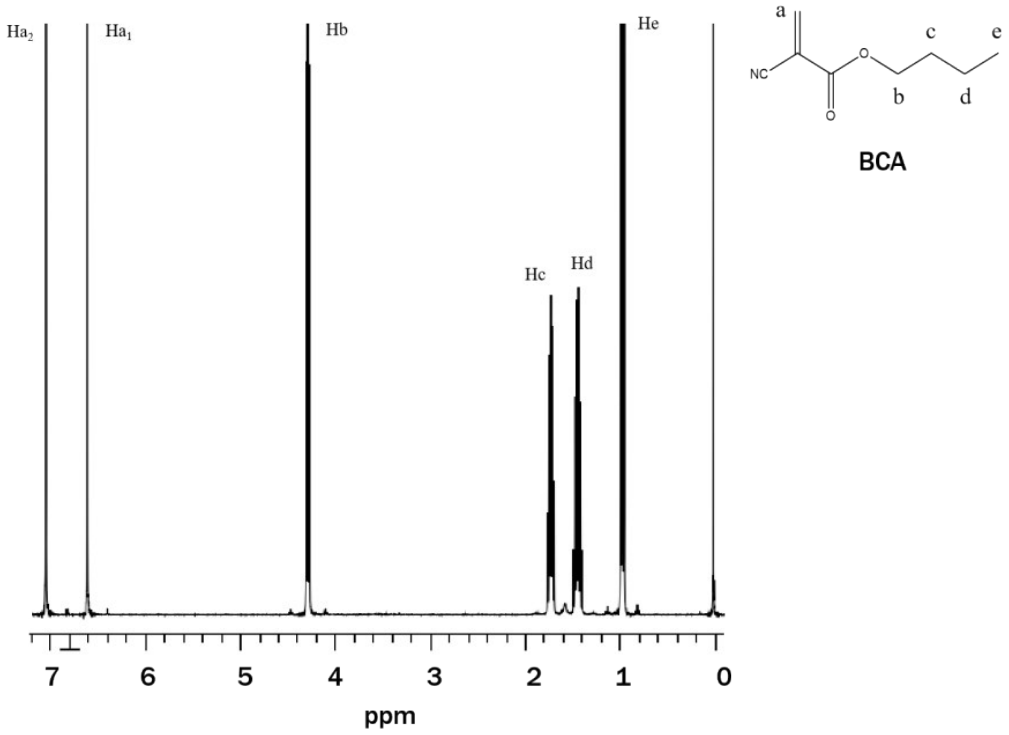
Scheme S2. Synthesis of 2-(2-methoxyethoxy)ethyl 2-cyanoacrylate (MECA). (i) Diethylene glycol monomethyl, tetrabutyl titanate, 8 h reflux. (ii) Piperdine, paraformaldehyde, 1,2-dichloroethane, 3 h azeotropic water removal. (iii) p-Toluenesulfonic acid, phosphoruspentoxide, hydroquinone, di-n-octylo-phthalate, prolysis; rectification.



Scheme S3. Synthesis of FITC-labeling 6-amino-1-hexanol cyanoacrylate. (a) Synthesis of 6-DMT-amino-1-hexanol. (i) C_3H_9ClSi, pyridine, room temperature, 12 h. (b) Synthesis of FITC-labeling 6-amino-1-hexanol cyanoacrylate. (ii) DIC, DMAP, DCM, room temperature, 6 h. (iii) CH_3COOH, DCM, room temperature. (iv) FITC, DCM, EtOH, room temperature. (v) Maleic anhydride, dimethylbenzene, EtOH, room temperature, 5 h.

The FITC-labeled 6-amino-1-hexanol cyanoacrylate was synthesized following a reported method in the literature[1] for evaluation of the metabolism and distribution of orally administered polyMECA. The product was mixed with MECA (97%, wt%) to prepare the resulting FITC-labeled copolymer.

(a)



(b)

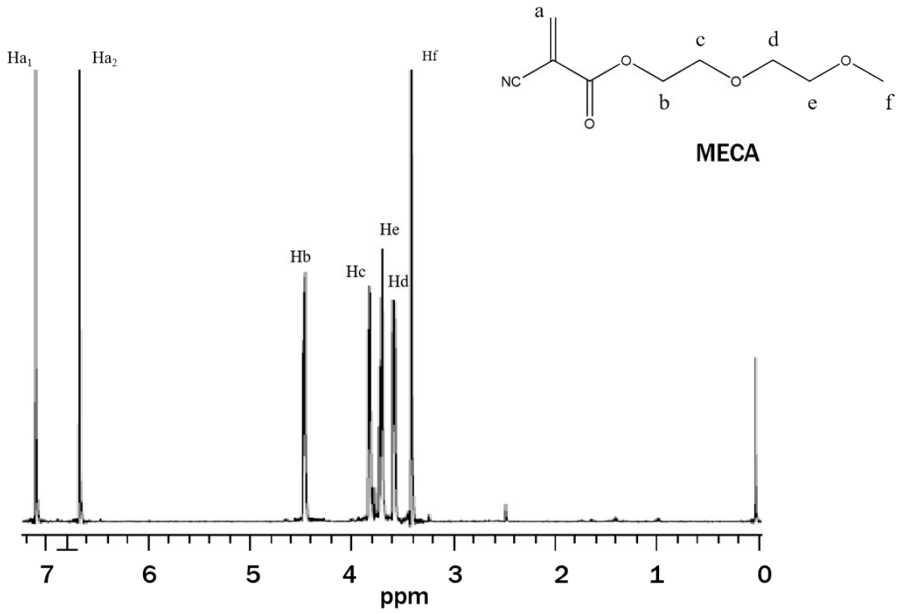


Fig. S1 ^{1}H-NMR spectra of BCA and MECA.

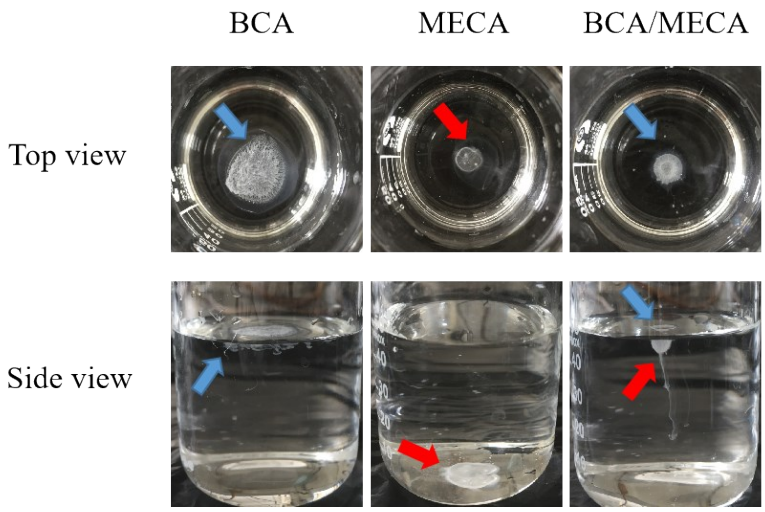
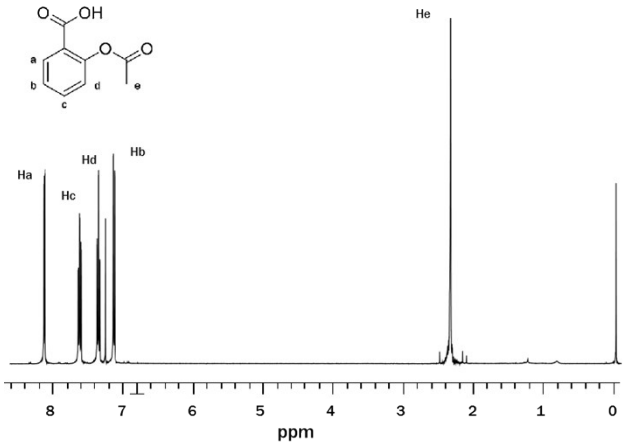


Fig. S2 Film formation in the BCA, MECA, and BCA/MECA groups. The blue arrows indicate hydrophobic film and the red arrows indicate solid glue blocks. Film forming tests were performed according to the national standards of the medical industry (YY/T 0729-2009, China). Briefly, a droplet of CA (50 μL) was gently dropped onto the surface of the fresh sodium bicarbonate solution (50 mL, 0.3 g/L) in a glass beaker (50 mL) at room temperature. Film formation of the monomers were observed at 1 min after addition. Results indicate that the BCA monomers polymerized into polymer films that floated on the solution surface. All MECA samples formed solid glue blocks that sank to the bottom. Only a portion of the BCA/MECA monomer samples formed floating films; the others slowly sank to the bottom. Alkoxy sidechain modification could endow the CA material with better hydrophilicity.

Table S1 Contact angles of the polyCA formulations

Sample	CA monomer composition	Contact angle(°)
S001	BCA	109.5 ± 3.57
S002	MECA	46.13 ± 1.31
S003	BCA/MECA	61.80 ± 0.98

(a)



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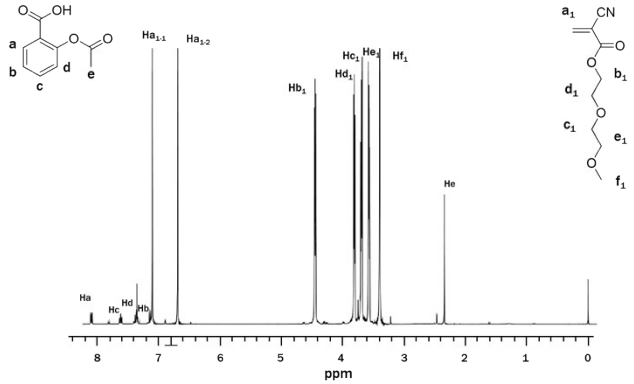


(c)

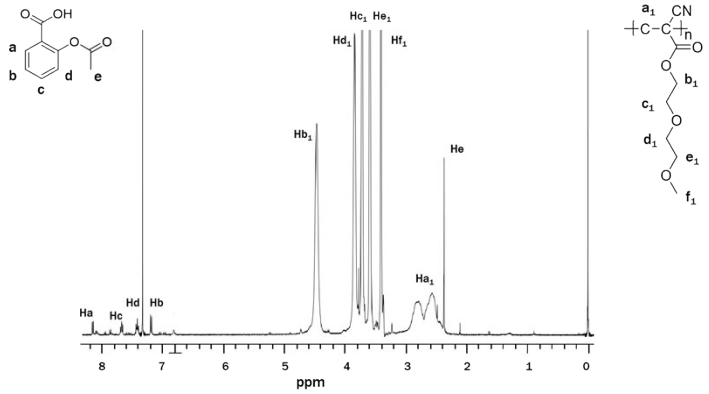


Fig.S3 ^{1}H-NMR spectra ($CDCl_3$) of ASA (a), ASA-MECA (b), and ASA-polyMECA (c) at 25℃.

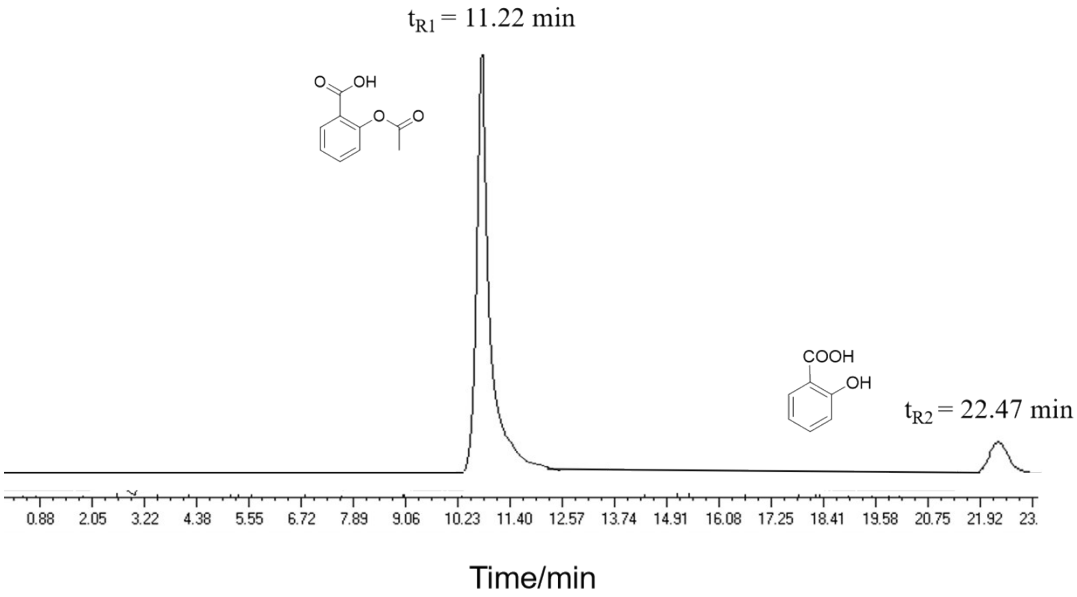
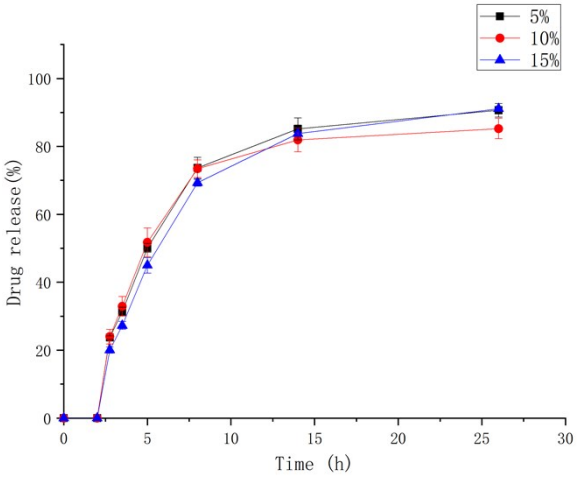


Fig. S4 *In vitro* drug release, as determined by HPLC. t_{R1} is the characteristic peak of aspirin and t_{R2} is the characteristic peak of salicylic acid.

(a)



（b）

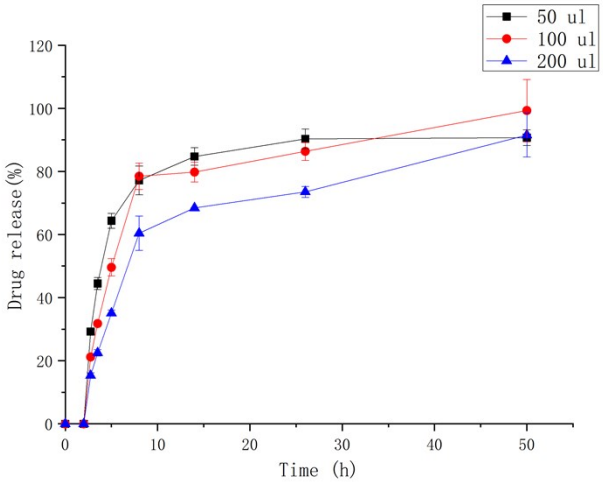


Fig. S5 *In vitro* profiles of ASA release from ASA-polyMECA-HPMCP under (a) different drug loading rates and (b) matrix volumes. Data are means ± SDs (n = 3).

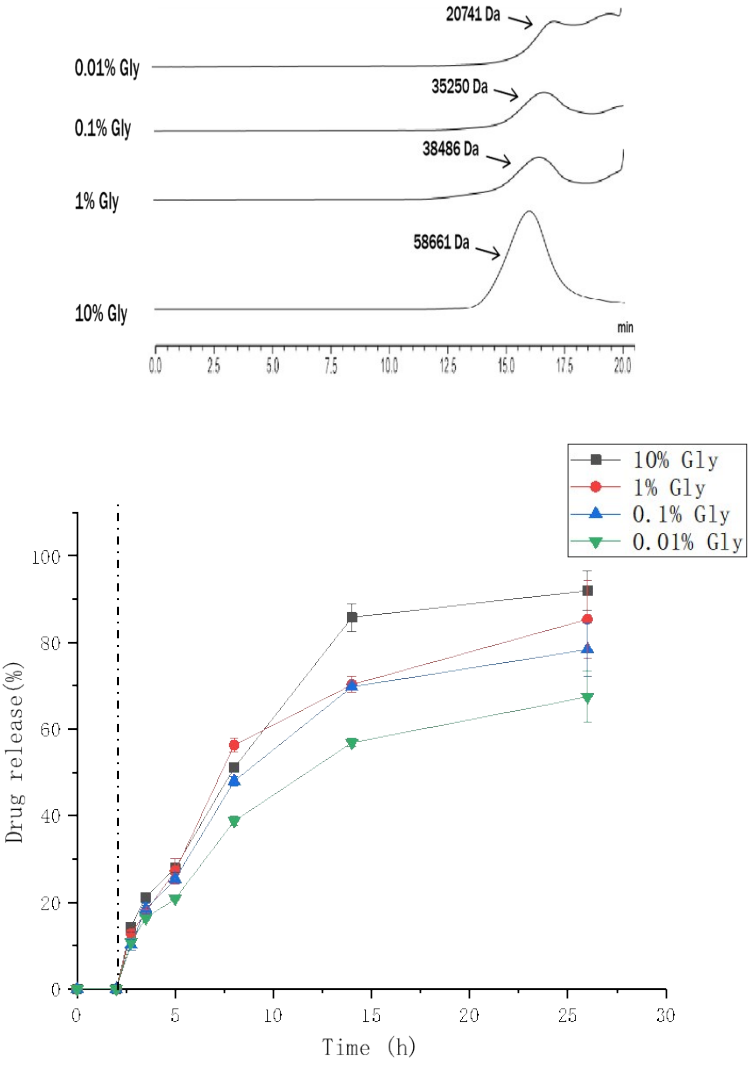


Fig. S6 The effects of (a) molecular weights of polyMECA on (b) the release capacity for ASA. The polyMECAs with increased molecular weight were achieved by adding initiator with increased concentration (0.01%, 0.1%, 1%, and 10% Glycine solution, separately), and the GPC chromatogram was used to determine the molecular weight (a). The dashed line in release profile (b) represents the change of medium pH from 1.2 to 6.8, and data are means ± SDs (*n* = 3).

Table S2 Shear tensile strength of polyBCA and polyMECA

Group	Shear tensile strength (kPa)
polyBCA	0
polyMECA	12.93 ± 1.16

Data are means ± SDs from six parallel experiments.

PolyMECA showed adhesive/sticky capability when smeared between two pieces of intestine. PolyBCA showed no sign of adhesion to the intestine.

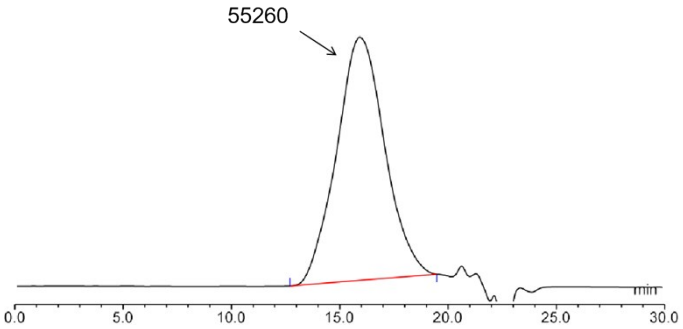


Fig. S7 GPC chromatogram of polyMECA.

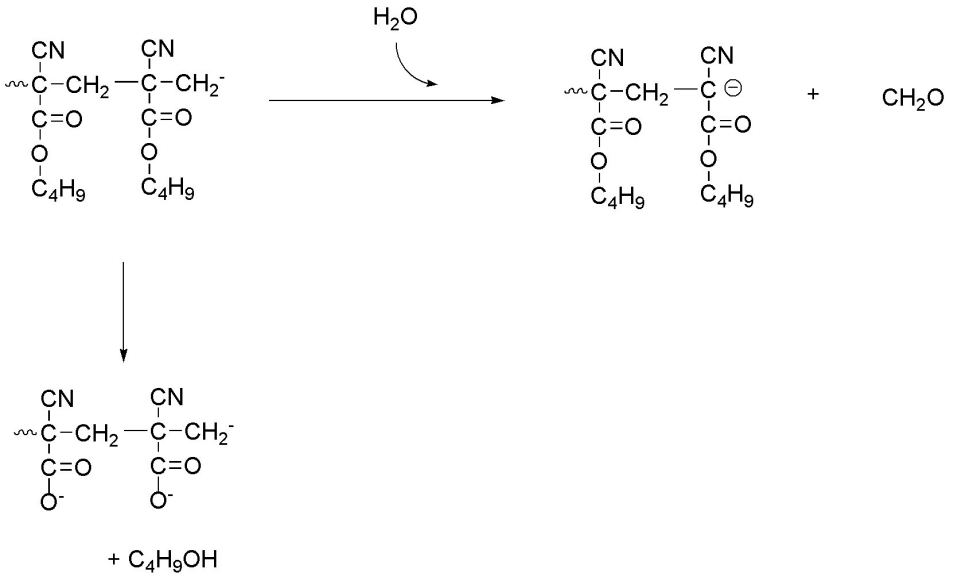


Fig. S8 Degradation mechanism of polycyanoacrylate.

Chemical analysis of the degradation products in an *in vitro* degradation test: Samples of polyMECA (100 μg) were placed in 50 mL stroke-physiological saline solution. The experiments were carried out at 37 ℃ with a 100-rpm shaking rate. Pre-column derivatization HPLC method was used for determination of free formaldehyde in fluid. 60mg of the derivatizing agent 2,4-dinitrophenylhydrazine (DNPH)was dissolved in 200mL of buffered saline (acetonitrile : acetate 50 : 50). This solution was used for formaldehyde standards derivatization and in sample preparation. Calibration levels 50, 40, 30, 25, 20, 15, 10, 5, 0 μg/ml were prepared by suitable diluting of the working standard in acetonitrile: water (50:50 v/v) in test tube containing 100 μL DNPH ; 25 μL of the solution was subjected to HPLC analysis and the correlation coefficient should be higher/better than 0.99. 100 μL degradation fluid was transferred to test tube and mixed with 150 μL of DNPH reagent. A large quantity of yellow precipitate was formed immediately. The mixture was centrifuged at 4000 rpm for 10 min and put the filtrate in a shaking water bath at 60 ℃ for 1h. After filtration of the warmed sample over membrane filter with pore size 0.45 μm, 25 μL of it was injected onto HPLC. Meanwhile, the base consumed by the ester hydrolysis was monitored by a titrimetric method. Addition of NaOH 0.1 N was used to keep the pH exactly at the preselected value (pH 6.5), and recorded the consumption of NaOH.

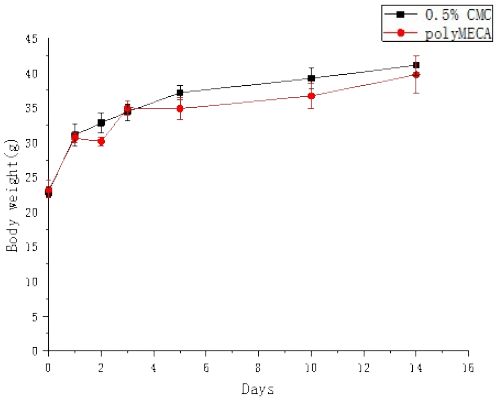


Fig. S9 Effect of polyMECA on body weight in the mouse acute toxicity study. Data are means ± SDs (n = 5).

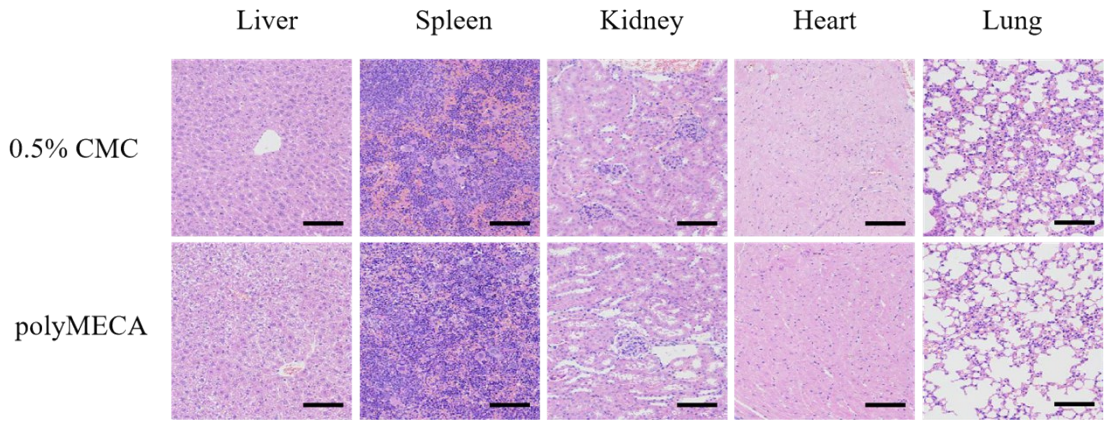


Fig. S10 Histopathological sections of major organs from the mouse acute toxicity study. The images were obtained under a Leica microscope at ×200 magnification. The scale bar is 100 μm.

REFERENCES

1. T. Zhang, Y. Tang, L. Xu and K. Liu, *Chem J Chin Univ*, 2016, **37**, 1168-1174.