Electronic Supplementary Material (ESI) for RSC Advances

Catanionic Vesicles from an Amphiphilic Prodrug Molecule: a New Concept of Drug Delivery System

1. ^{1}H-NMR Measurements. The NMR data were recorded on a Bruker Avance 600 spectrometer operating at 600 MHz at room temperature. Amlodipine, oleic acid and amlodipine prodrug were freshly dissolved in 0.5 mL DMSO-d_6 in 5 mm in diameter NMR tubes, respectively. Chemical shifts were reported in ppm with respect to tetramethylsilane.

^{1}H-NMR spectra of amlodipine, oleic acid , amlodipine prodrug and the molecular structure with the proton signs are given in Figure S1 to further confirm the chemical structure of the prodrug. Figure S1a shows ^{1}H-NMR spectra of amlodipine, the peaks at δ 3.43 ppm (2H) and 2.73 ppm (2H) are assigned to the protons bound to the carbon atoms next to $–NH_2$ or oxygen atom, namely, the protons of H13, H12. Because oxygen atom has stronger electronegativity than that of nitrogen atom, H12 close to oxygen atom has lower chemical shift than that of H13. The signals come from protons of $–NH_2$ may be covered by that of H_2O at 3.32 ppm. Figure S1b shows the typical ^{1}H-NMR spectra of oleic acid. According to the similar analysis for amlodipine molecules, the peak assignments of the oleic acid molecule are as follows: the peaks at 2.18 ppm can be assigned to the protons bound to the carbon atoms next to the –COOH group, that is the protons of the $–CH_2$ groups (Hb). At the same time, signal appeares at 11.98 ppm, corresponding to the proton on the carboxyl group. It can be seen from the ^{1}H-NMR spectra of amlodipine prodrug (Figure S1c) that the peak for active protons of –COOH disappears. The peaks for H13 and H12 are shifted to a higher field, H13 from 2.73 ppm to 2.78 ppm and H12 from 3.43 ppm to 3.47 ppm. For amlodipine prodrug, $–NH_2$ transformed into $–NH_3^+$, which lowering the electron density around H13 and H12 and weakening the local shielding. On the contrary, the chemical shift for Hb turned into 2.14 ppm, due to the higher electron density of $–COO^-$.

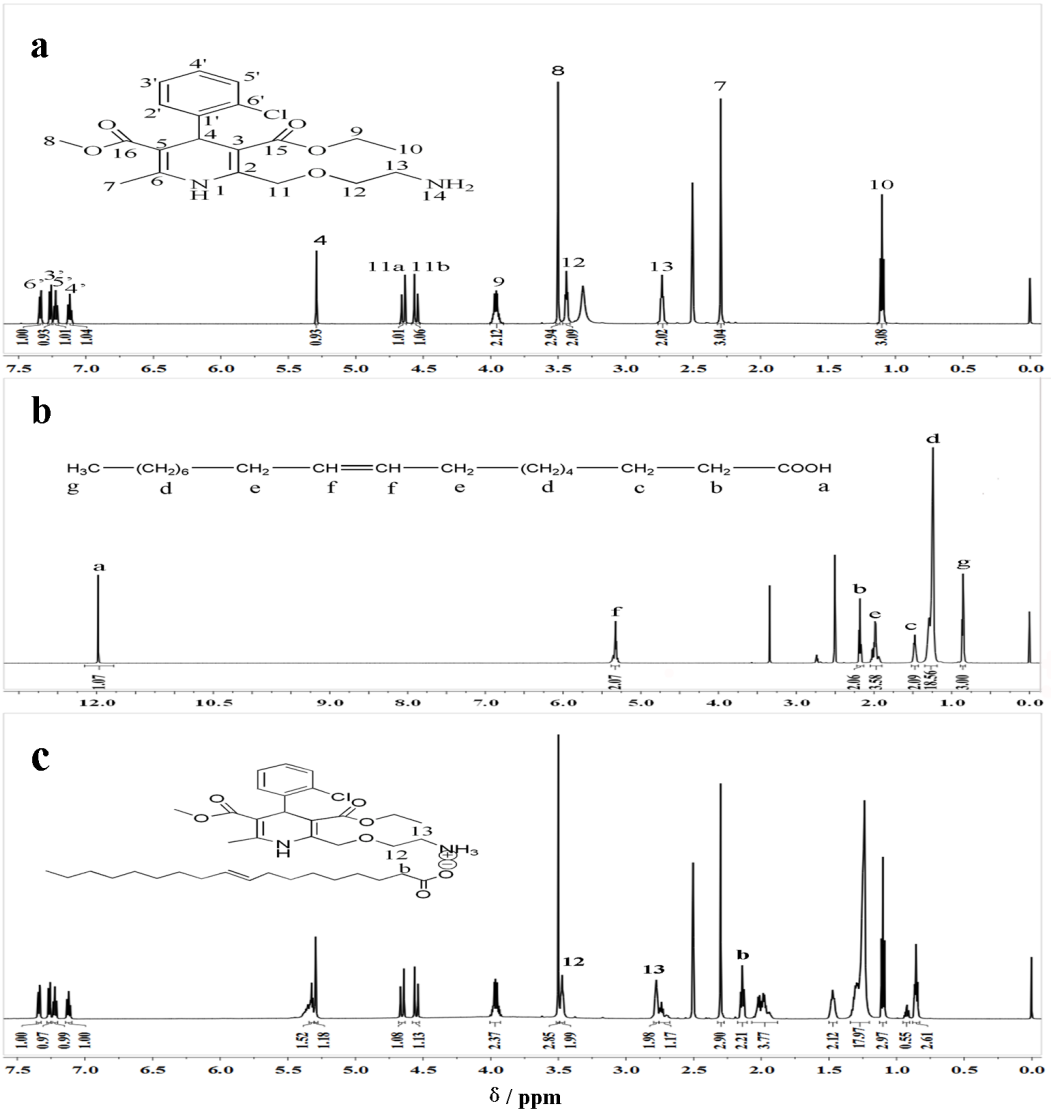

Figure S1. [1]H-NMR spectra of pure amlodipine (a), pure oleic acid (b), the amlodipine prodrug (c).

2. Differential Scanning Calorimetry (DSC). DSC measurements were taken with CDR-4P (Shanghai Precision and Scientific Instrument Co., Ltd. China). Weighed samples of 10 mg were placed in aluminum pans and the samples were scanned from 30 ℃ to 300 ℃. The heating rate was 10 °C/min.

Differential scanning calorimetric analyses were carried out on amlodipine, oleic acid and the prodrug molecules. The results are shown in Figure S2. The thermal curve of amlodipine (Figure S2a) exhibits a sharp endothermal peak with melting temperature of 142 ℃, which is in good agreement with the report of 142.32 ℃.[1] There are no peaks for oleic acid in the temperature range of 30-300 ℃ (Figure S2b),

which agrees well with the reported results in the literature.[2,3] The reported results demonstrate oleic acid exhibits two endothermic peak at about -5 ℃ and 12℃, corresponding to the melting of the α-form of oleic acid and the solid-solid transition from γ to α phase, respectively. For the amlodipine prodrug molecules (Figure S2c), a sharp endothermal peak appears at 74.8℃ indicating the phase transition occurs, which could be assigned to the melting temperature of the prodrug molecules. Overall, for the prodrug sample, the sharp endothermal peak (melting temperature) at 142 ℃ of the amlodipine drug disappears while new sharp endothermal peak (melting temperature) at 74.8℃ appears. This indicates the formation of new compound. Therefore, DSC results further prove the formation of amlodipine prodrug based on the proton transfer reaction between the carboxyl of oleic acid molecules and the amine of the amlodipine molecules.

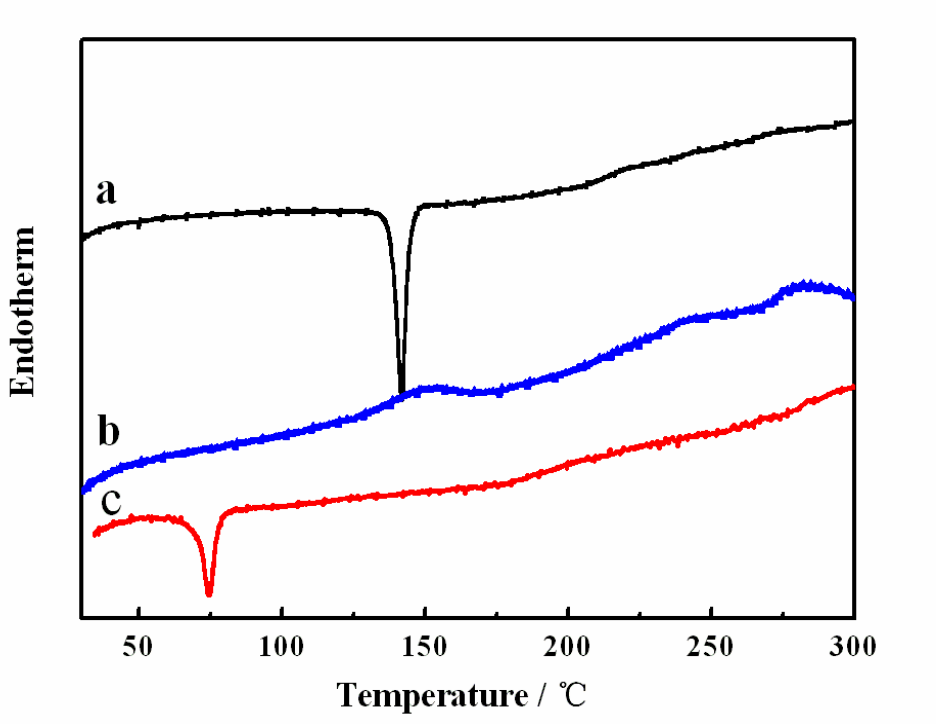

Figure S2. DSC curves of (a) pure amlodipine, (b) oleic acid and (c) the amlodipine prodrug.

1 Y. Sun, L. Fang, M. Zhua, W. Li, P. Meng, L. Li, Z. He, *Int. J. Pharm.* 2009, **382**,

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2 S. Wartewig, R. Neubert, W. Rettig, K. Hesse, *Chem. Phys. Lipids.* 1998, **91**, 145.

3 P. Tandonl, G. Förster, R. Neubert, S. Wartewig, *J. Mol. Struct.* 2000, **524**, 201.