Electronic Supplementary Material (ESI) for Journal of Materials Chemistry B.

Supporting Information

Codelivery of doxorubicin and sodium tanshinone IIA sulfonate using multicompartmentalized vesosomes to enhance synergism and prevent doxorubicin-induced cardiomyocyte apoptosis

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1. Uptake of free drug combination, drug combination in liposomes, and drug combination in MCVs

Liposomes and MCVs can promote the uptake efficiency of Dox, because the internalization of liposomes into active cells is slower but easier than free drugs.[1] Dox were loaded in liposomes and MCVs, and compared with negative control and free Dox to determine their uptake by A549 cells, as shown in Fig. S1.

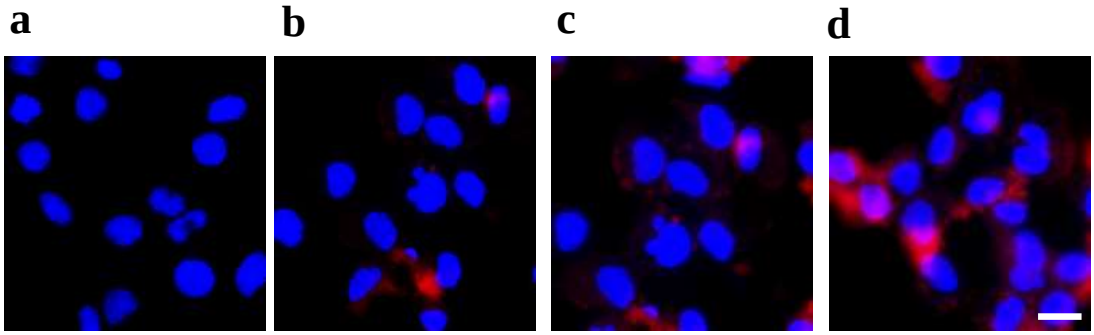

Fig. S1 Uptakes of Dox of different carriers. (a) Negative control, (b) free Dox, (c) Dox in liposomes, and (d) Dox in MCVs. The images were merged images of DAPI channel and Dox channel. The scale bar is 50 μm.

2. Determination of drug concentration in MCVs

Calibration curves of DOX and STS are shown in Fig. S2 and S3 respectively.

The calibration fitting equation of Dox is:

$$y = 0.0044\ (0) + 0.071\ (0)\ x \quad (1)$$

The calibration fitting equation of STS is:

$$y = 0.0016\ (0) + 0.066\ (0.004)\ x \quad (2)$$

The values of intercepts and slopes are expressed as mean value (standard error) in both equations.

R^2 value are both 0.99.

According to the calibration curves, the concentrations of Dox and STS in free drugs were 1.00 ± 0.04 μg mL^{-1} and 1.00 ± 0.06 μg mL^{-1}, respectively. The same amount of drugs were used to prepare the drugs loaded vesosomes. After purified by Saphadex, vesosomes were break down by Triton X-100 and vortex. The suspensions were filtered by dialysis bag. The supernatants were tested by UV-vis spectrameter. Dox was tested at 495 nm, and STS was tested at 280 nm. The concentrations of Dox and STS in MCVs were 0.490 ± 0.043 μg mL^{-1} and 0.520 ± 0.026 μg mL^{-1} respectively.

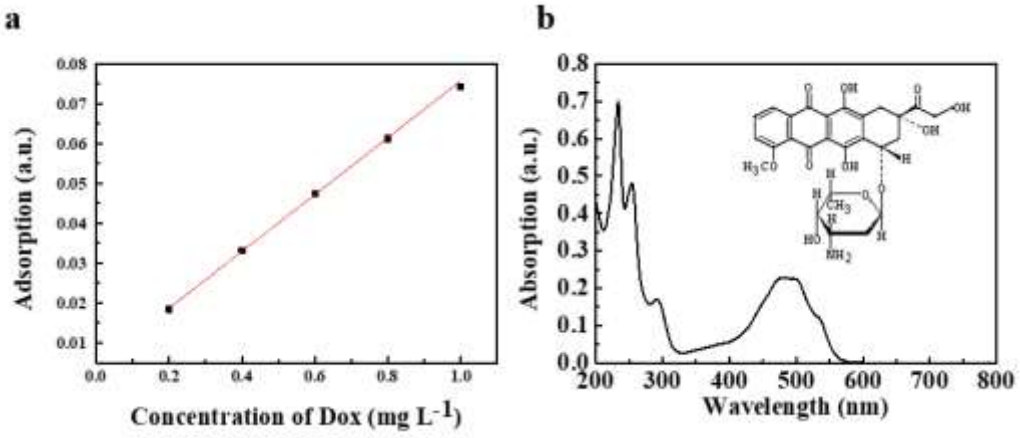

Fig. S2 a) Calibration curve of DOX. b) UV-vis absorption spectrum of DOX. The inset is the structural formula of DOX.

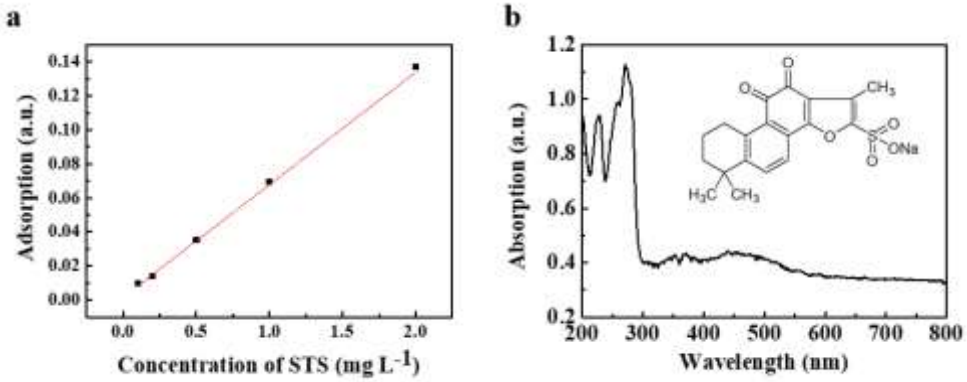

Fig. S3 a) Calibration curve of STS. b) UV-vis absorption spectrum of STS. The inset is the structural formula of STS.

3. Quantitative diagnostic plot

Isobolograms in Fig. S4 demonstrate the comparable effect with equivalent dose of individual STS or Dox. As shown in Fig. S4(c), the equivalent lines represent additive effect, while the area above the line represents antagonism, and the area below the line represents synergism. As to MCVs, the isobologram indicates that more data points drop in the synergistic area, and both liposomes and MCVs have dose reduction of Dox compared to free drug.

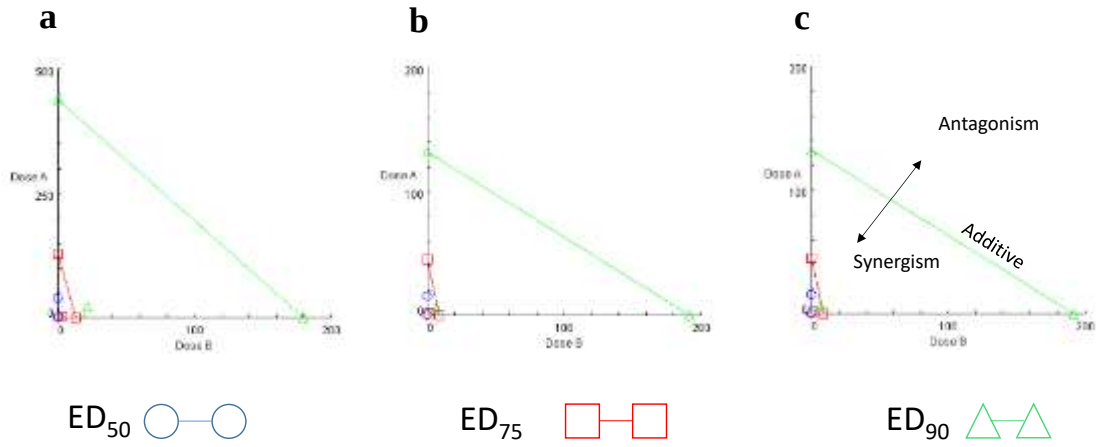

Fig. S4 Isobolograms of (a) free drug combination, (b) drug combination in liposomes and (c) drug combination in MCVs. Dose A stands for dose of STS and Dose B stands for dose of Dox in each experiment. Blue circle, red square and green triangle represent the experimental data. Blue, red and green lines represent isobolograms of effect dose (ED) of 50%, 75% and 90% inhibitory efficacy, respectively.

4. Cell viability of H9c2 cardiac cells

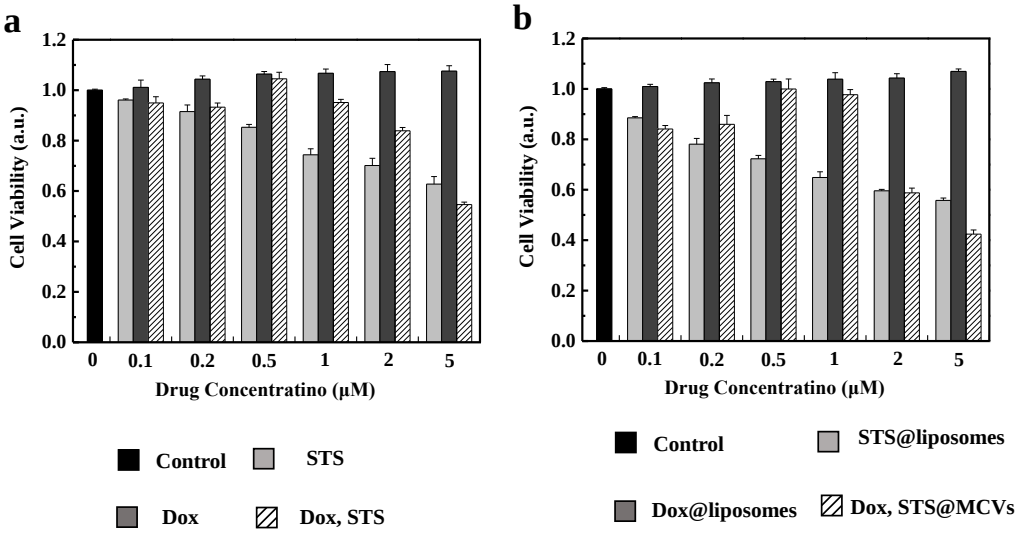

Fig. S5 Cytotoxicity of co-delivery of Dox and STS for H9c2 cells. (a) Cells were treated with free Dox or STS alone, or co-delivery of Dox and STS in the molar ratio of 1:1 for 48 h. (b) Cells were treated with Dox or STS in liposomes, and co-delivery in MCVs for 48 h. Data represent the means ± standard deviation, n = 3.

Reference

[1] K. M. Camacho, S. Menegatti, D. R. Vogus, A. Pusuluri, Z. Fuchs, M. Jarvis, M. Zakrewsky, M. A. Evans, R. Chen, S. Mitragotri, *J. Controlled Release* **2016**, *229*, 154-162.