Acid-Labile Liposomes Constructed with Polyacrylic Acid (PAA) Modified Phospholipids

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INTRODUCTION

Liposomes have been studied as pH triggered drug release systems, which have a large internal volume, are biocompatible and can be easily taken up by tumor cells. In the past years, polymer modified lipids were applied to modify the stabilization and sensitivity of liposomes. The intrinsic low pH of endosomes has attracted people's interest on pH-triggered drug release. Acid-labile organic molecules and polymeric particles have also been reported in drug delivery. [1]

Herein, we report that polyacrylic acid (PAA) modified dioleoylphosphatidyl-ethanolamine (DOPE) is a promising material in drug release systems. 2-(Dodecylthiocarbonothioylthio)-2-methylpropionic acid modified DOPE (CTA-DOPE) served as a chain transfer agent for reversible addition-fragmentation transfer polymerization with the crosslinking of acid-labile linking molecules. [2]

EXPERIMENT

PAA-DOPE (Mw≈4500) was mixed with dipalmitoylphosphocholine (DPPC) to form liposomes (PAA-DOPE:DPPC=1:100, mol/mol, 80～120 nm) containing doxorubicin. 2,2'- (Propane-2,2-diylbis(oxy)) diethanamine wasprepared as an acid labile crosslinker (1,6-hexanediamine as control), and used to crosslink PAA on the surface of the liposomes. Release of doxorubicin (DOX) at pH of 5 and 7 was tested with fluorescence spectroscopy. With the increase of acidity of the solution, the release rate and released amount are gradually increased. Cell viability tests were performed showing that the liposomes without DOX are biocompatible.

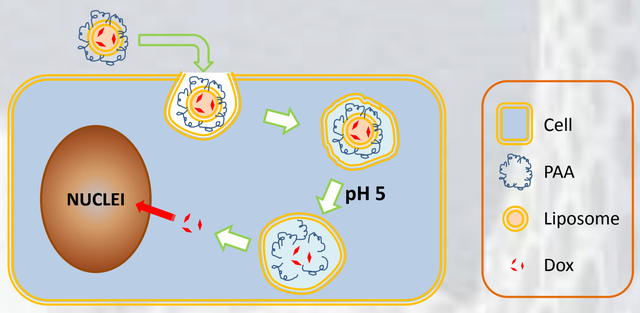

Figure 1. Scheme of liposomes up-taken by cells

RESULTS AND DISCUSSTION

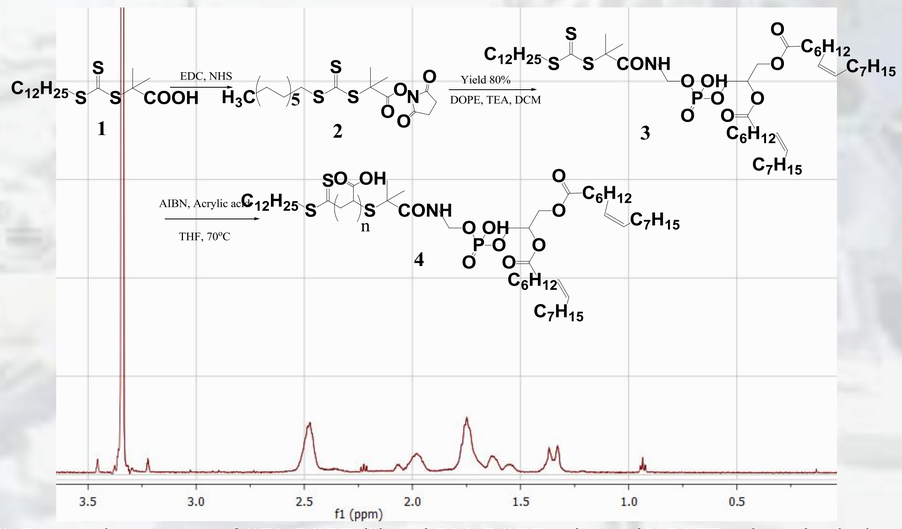

Figure 2. Preparation process of CTA-DOPE (**3**) and PAA-DOPE polymer (**4,** RAFT polymerization) and the 1-H NMR of PAA-DOPE.

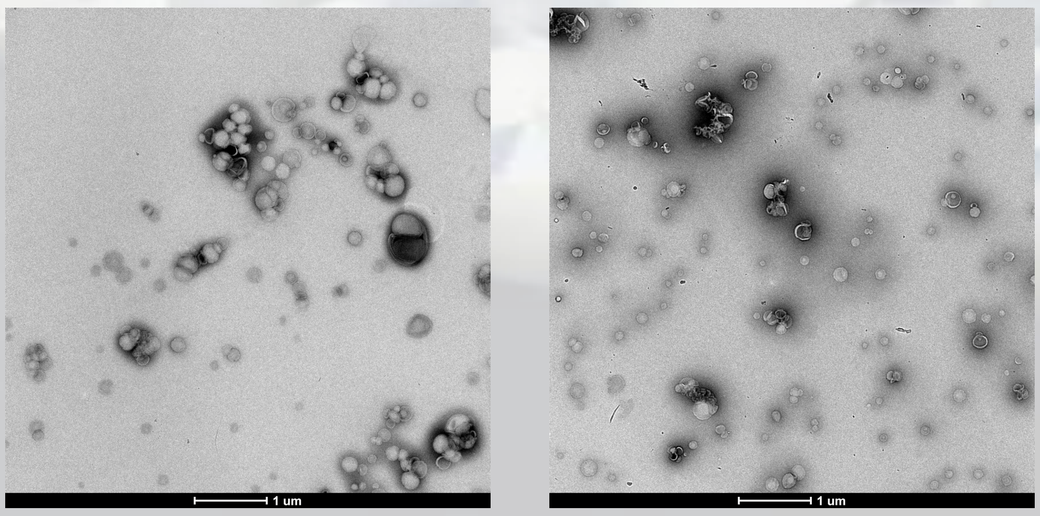

Figure 3. TEM images of acid-labile (left) and non-acid-labile liposomes(right), both samples are liposomes ranges mainly from 100-200 nm.

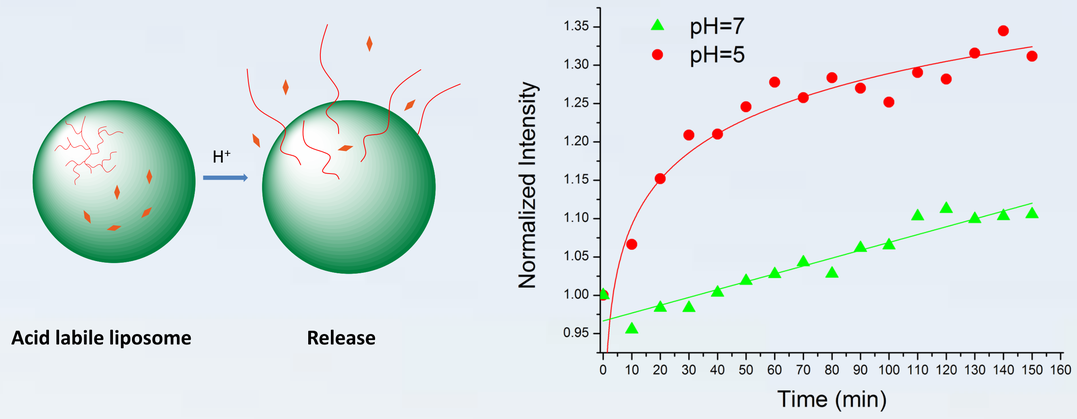

Figure 4. Scheme of acid-labile release(left) and release profiles of acid-labile liposomes at pH 5 and 7showing that the release goes faster with the decreasing of pH values

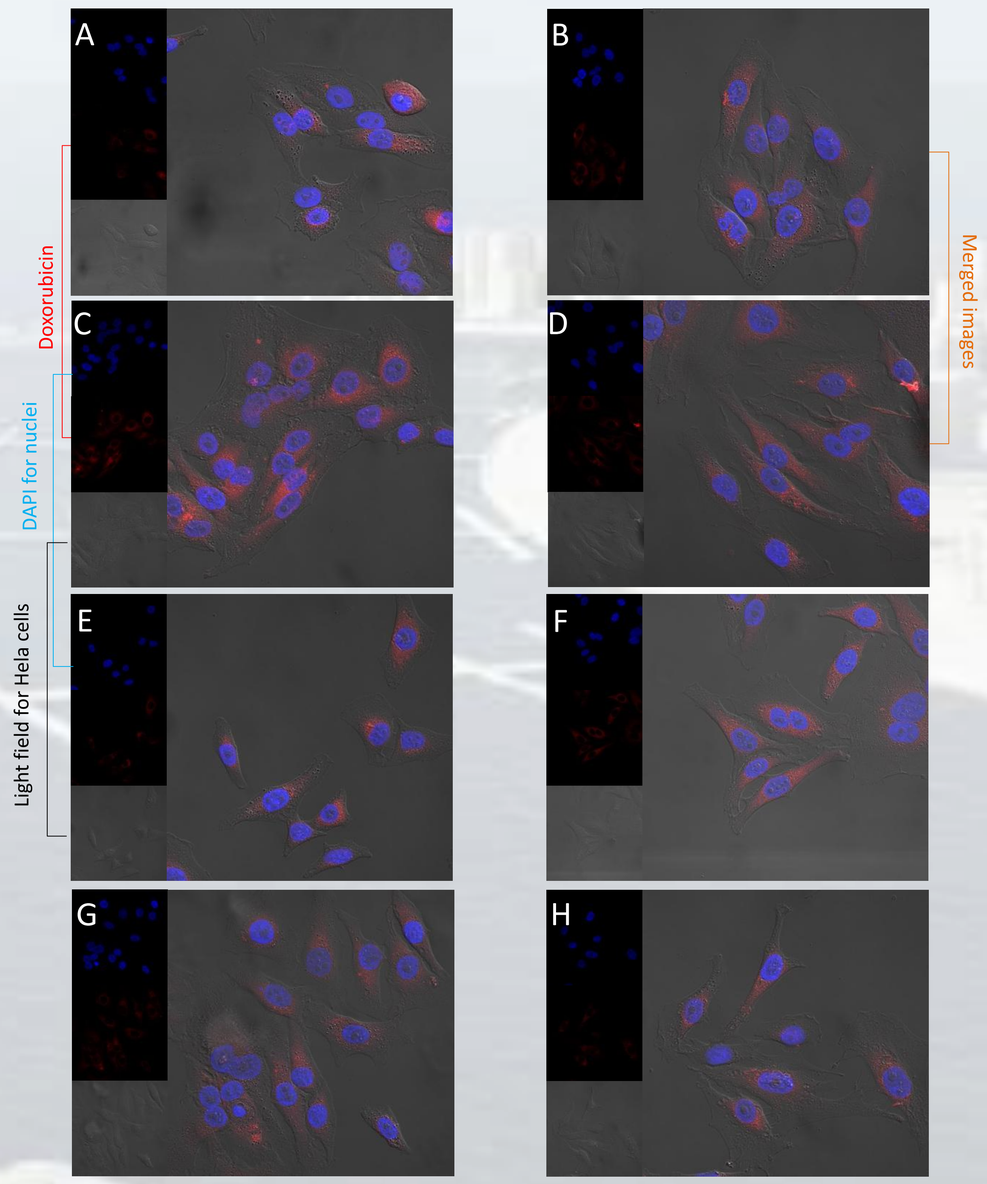

Figure 5. CLSM images of liposomes incubated with Hela cells (DAPI stained): A.B.C.D. Acid-labile liposomes (ALLs) for 5 min, 15min, 30 min and 60min; D.E.F.G. Non-acid-labile liposomes (NALLs) for 5min, 15 min, 30 min and 60 min. ALLs have a brighter fluorescence of dox than NALLs, which means that more release was there in the cells incubated with ALLs.

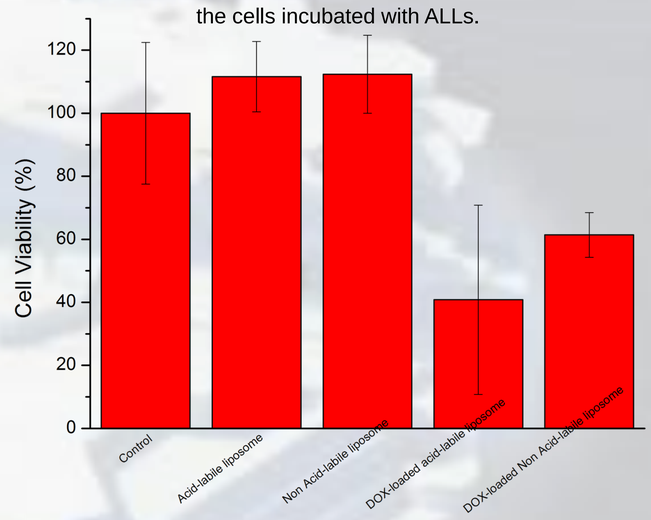

Figure 6. MTT assay results showing that the cell viability of controlled sample, PAA-AL and PAA-NAL sample with and without dox loaded.

CONCLUSION

PAA-DOPE based liposomes are approved to be effective acid-labile drug delivery systems. *In-vitro* tests show that such liposomes are promising with a good acid sensitivity.

REFERENCES

[1] J. Shin, P. Shum, D.H. Thompson, Acid-triggered release via dePEGylation of DOPE liposomes containing acid-labile vinyl ether PEG–lipids, J. Control. Release 91 (2003) 187-200.

[2] S.E. Paramonov, E.M. Bachelder, T.T. Beaudette, S.M. Standley, C.C. Lee, J. Dashe, J.M.J. Fréchet, Fully acid-degradable biocompatible polyacetal microparticles for drug delivery, Bioconjugate Chem. 19 (2008) 911-919.

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