Triggered release of doxorubicin from temperature sensitive poly(N-(2-hydroxypropyl)-methacrylamide mono/dilactate) grafted liposomes

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ABSTRACT SUMMARY

Liposomes grafted with chol-pHPMA were developed to release doxorubicin (DOX) at elevated temperature generated by high intensity focused ultrasound (HIFU) exposure. The release characteristics of these liposomes are tunable by varying the molecular weight, the copolymer composition and the grafting density.

INTRODUCTION

Liposomes are used as carriers for the delivery of cytostatic drugs. The efficiency of these liposomes can be increased via triggered drug release. High drug concentrations at the tumor site can be reached when temperature sensitive liposomes release their content during hyperthermia¹. The aim of this project is to graft liposomes with a temperature sensitive polymer to induce temperature triggered release of DOX (Figure 1). These polymers have a cloud point (CP)², above which, once grafted on the surface of a liposome, the polymer will dehydrate and interact with the bilayer of the liposome, resulting in membrane permeabilization and DOX release³. In the present study, the effect of polymer characteristics (copolymer composition and polymer molecular weight) and grafting density on the release of DOX was investigated. A stable formulation with fast release kinetics at elevated temperatures and from which DOX release can be induced after HIFU exposure is preferred.

EXPERIMENTAL METHODS

Poly(N-(2-hydroxypropyl)methacrylamide mono/dilactate) was synthesized with thiocholesterol (chol-pHPMAlac) as chain transfer agent (CTA) (Figure 2). The CP was tailored by the mono:dilactate ratio and the polymer molecular weight via the monomer:CTA ratio. These polymers were incorporated in the liposome bilayer via the cholesterol anchor followed by DOX loading. The release of DOX from these chol-pHPMAlac grafted liposomes was measured at elevated temperatures and after HIFU exposure.

Figure 1 Schematic representation of heat triggered DOX release from liposomes grafted with chol-pHPMAlac.

Figure 2 poly(N-(2-hydroxypropyl) methacrylamide mono/dilactate
RESULTS AND DISCUSSION

A good correlation between the release-onset temperature of the liposomes and the CP of chol-pHPMAAlac was found. However, release took place ~20 degrees higher than the CP of chol-pHPMAAlac. Likely at the CP, the dehydration and thus hydrophobicity is insufficient to penetrate and permeabilize the liposomal membrane. Liposomes grafted with chol-pHPMAAlac with a CP of 11.5 °C released 89% DOX within 5 minutes at 42 °C while for the liposomes grafted with chol-pHPMAAlac with a CP of 25.0 °C, a temperature of 52 °C was needed to obtain the same extent of DOX release (Figure 3).

![Figure 3 DOX release from liposomes grafted with chol-pHPMAAlac (CPs of 11.5 to 32.0 °C).](image)

At a fixed copolymer composition, an increase in molecular weight from 6.5 to 14.5 kDa decreased the temperature at which DOX was released with a release-onset temperature from 52 to 42 °C.

Liposomes grafted with 5% chol-pHPMAAlac exhibited a rapid release at a temperature increase while at a grafting density of 2 and 10%, the liposomes were less sensitive to an increase in temperature.

Chol-pHPMAAlac grafted liposomes released DOX nearly quantitatively after pulsed wave HIFU (Figure 4).

![Figure 4 DOX release from liposomes grafted with chol-pHPMAAlac with a CP of 19.0 °C and a Mn of 10.0 kDa after exposure to PW-HIFU with an acoustic power of 20 W and a duty cycle of 20%.](image)

CONCLUSION

The release of DOX from liposomes grafted with thermosensitive polymers of N-((2-hydroxypropyl)methacrylamide mono/dilactate can be tuned by the polymer characteristics and grafting density of chol-pHPMAAlac, making these liposomes attractive for local drug delivery using hyperthermia.

REFERENCES


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