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Sequentially dual-targeting vector with nano-in-micro structure for improved docetaxel oral delivery in vivo

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Abstract:
In this study, we constructed a novel vector with nano-in-micro structure to improve the oral absorption of docetaxel (DTX) by sequentially dual-targeting functions toward intestine and sodium-dependent multivitamin transporter based on entrapping biotin-modifed micelles into alginate microparticles (Alg-BioPf-M). A series of characteristics of this system was investigated, such as drug release, cellular uptake, transport pathway and the comprehensive *in vivo* studies including pharmacokinetic studies, anti-tumor activity and toxicity study. The bioavailability of DTX-loaded Alg-BioPf-M was 27.4- fold higher than that of free DTX after oral administration and achieved superior tumor inhibition of 84.6% against sarcoma 180 tumors. These results demonstrated that the Alg-BioPf-M was a promising vector for oral delivery of DTX.

Introduction

Oral delivery is concerned to be a preferred route for cancer treatment when compared with intravenous administration owing to the innate compliance. Unfortunately, the oral bioavailability of DTX is extraordinary low due to many factors [1]. Recently, the application of nanocarriers in drug delivery has been considered as a new approach to enhance the oral absorption of drugs with low bioavailability [2]. It also has been shown that ligand-mediated active endocytosis is beneficial to improve drug absorption in the intestinal tract [3]. Here we developed a sequentially dual-targeting system for DTX oral delivery. As shown in Figure 1, this system displayed a nano-in-micro structure with two different targeting sections. One referred to alginate-based microscaled carriers with an enteric targeting function, which could deliver DTX to the active absorption site of intestine as much as possible with little waste in acidic gastric juice. The other was biotin attached on the surface of DTX-loaded nanomicelles, which was expected to improve DTX absorption via active targeting toward SMVT in intestinal epithelial cells.

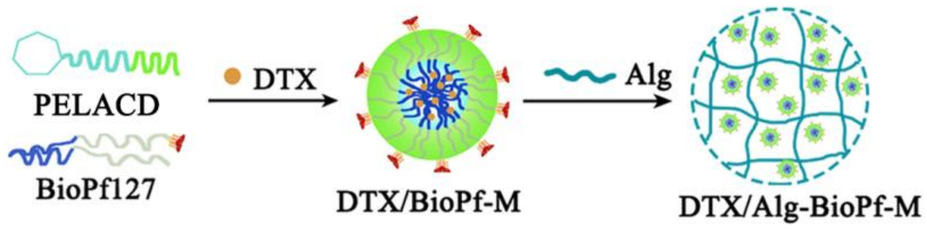

Fig. 1 The nano-in-micro structure of DTX/Alg-BioPf-M

Synthesis Route of BioPf127 and PELACD

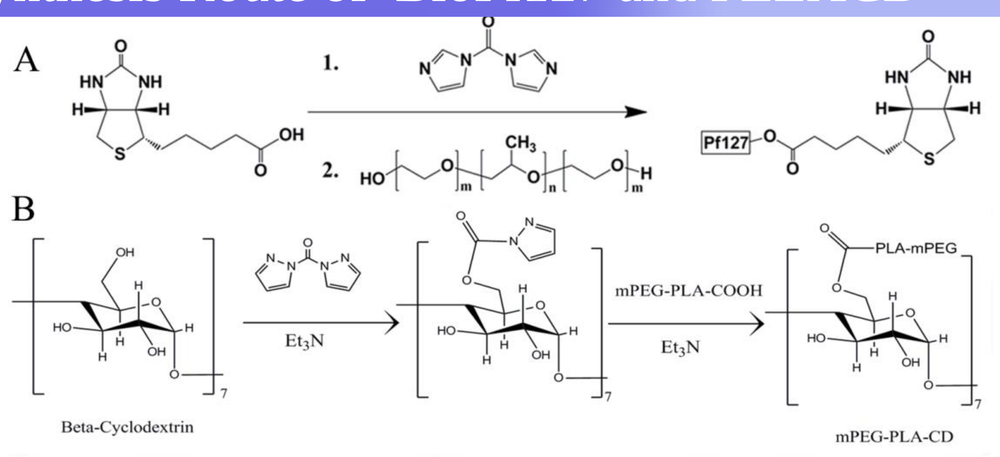

Fig.2 Synthesis route of (A) BioPf127 and (B) PELACD.

Characterization of DTX loaded-micelles

Micelle	BioPf127	30:10 [b]	10:10	5:10	1:10	0:10
LC% [a]	0.75±0.06	1.51±0.05	1.61±0.06	1.68±0.07	1.92±0.05	1.94±0.07
EE%	37.5±2.59	75.7±2.6	80.6±3.1	84.1±3.3	96.1±2.6	96.9±3.4
CMC (μg/mL)	39.0	13.8	3.7	3.2	2.0	1.2

Table 1. Drug loading content (LC) and drug encapsulation efficiency (EE) of DTX-loaded micelles (mean ± SD, n = 3).
a) The theory LC was 2%
b) The weight ratio of BioPf127 to PELACD

Release behavior of Alg-BioPf-M

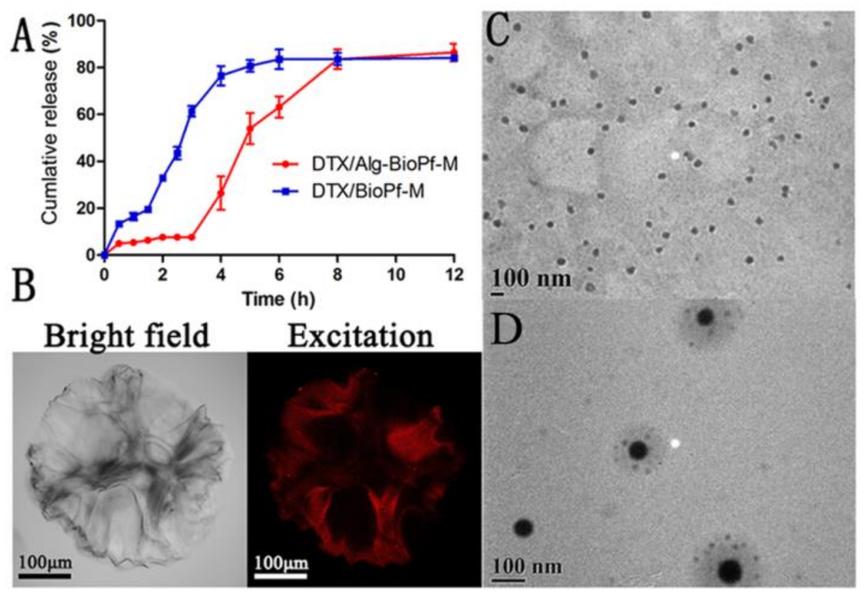

Fig. 3 (A) The released profile in pH 1.2 for 2 h and pH 6.8 for 22 h. (B) The morphology of DOX/Alg-BioPf-M by CLSM.(C) TEM images of DTX/BioPf-M. (D) TEM images of micelles released from Alg-BioPf-M.

Whole body fluorescence images

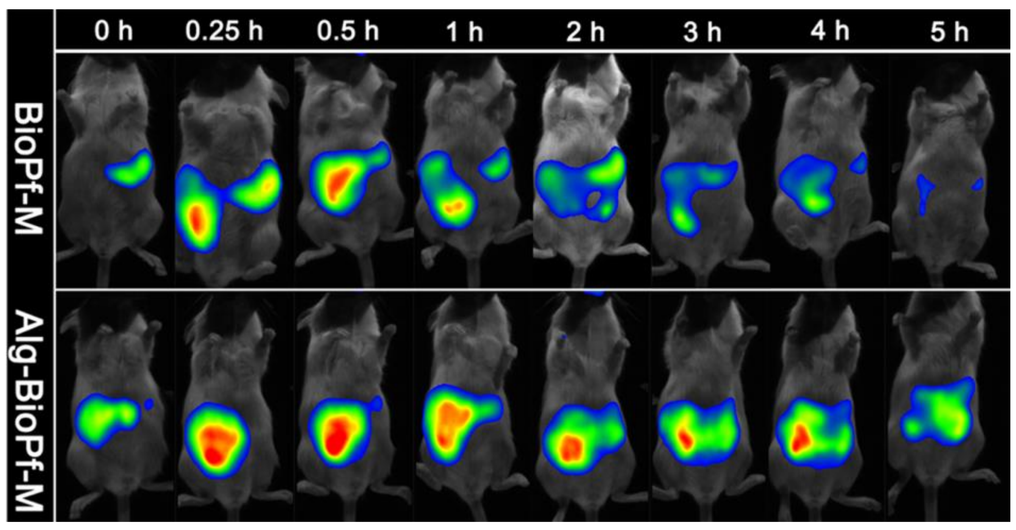

Fig. 4 Oral administration of ICG/BioPf-M and ICG/Alg-BioPf-M at a dose of 2 mg/kg ICG.

In vivo tumor inhibition study

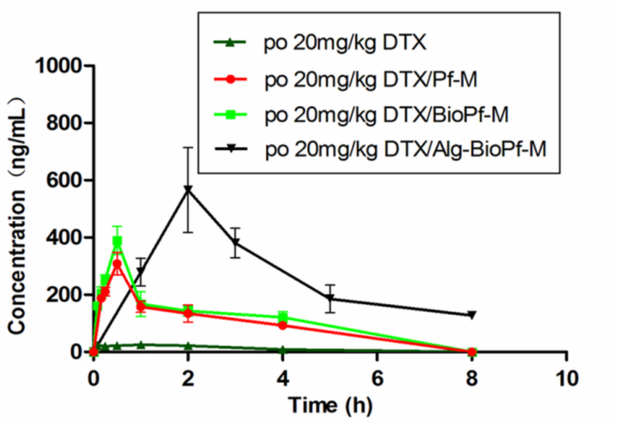

Fig.5 Oral administration of free DTX, DTX/Pf-M, DTX/BioPf-M and DTX/Alg-BioPf-M at dose of 20 mg/kg. (n=3).

Conclusions

We successfully constructed a novel sequentially dual-targeting system for DTX oral delivery with significantly enhanced bioavailability and antitumor efficacy . the pH-responsive Alg-BioPf-M release of BioPf-M specifically in intestine and cellular uptake of BioPf-M was improved by receptor-mediated endocytosis pathway

Acknowledgement

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References

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