CYCLODEXTRIN POLYMERS AS A TEMOPORFIN NANOCARRIER

Yakavets I.V.[1,2], Guereschi C.[1,2], Kravchenko I.E.[3], Borisov K.N.[3], Lassalle H.-P.[1,2], Bolotine L.N. [1,2]

[1] *Institut de Cancérologie de Lorraine, Vandoeuvre-lès-Nancy, France*
[2] *CRAN, CNRS, Université de Lorraine, Nancy, France*
[3] *Belarussian State University, Minsk, Belarus*

Supramolecular delivery systems are considered as one of the most versatile strategies in pharmaceutics. Cyclodextrins (CDs) represents an excellent example of a supramolecular system. Owing to a toroidal structure with an inner hydrophobic cavity and outer hydrophilic surface, CDs can improve the chemical and physical stability of drugs through the formation of drug/CD complexes, as well as modulate drug biodistribution when binding is strong enough [1]. Recently, our group reported on the extremely strong binding of β-CD derivatives to temoporfin (mTHPC, medicinal product name: Foscan®) [2]. It worth noting that mTHPC is one of the most potent clinically approved photosensitizers (PSs) for photodynamic therapy (PDT) of head and neck cancer. A high affinity of β-CD derivatives to mTHPC allows altering mTHPC distribution *in vitro* in 2D monolayer cells and 3D tumor spheroids as well as xenografted mice *in vivo* [3,4]. Also, CDs provide a unique opportunity for deep PS penetration in 3D multicellular tumor spheroids [3]. However, parental administration of CD/mTHPC complexes is hindered by the rapid CD excretion from the circulating system and quick drug release upon the dilution of complexes. Meanwhile, hyper-crosslinking of CD monomers *via* epichlorohydrin results in the formation of solid porous nanoparticles within a three-dimensional network. Such CD polymers could encapsulate drugs forming both inclusion and noninclusion complexes with drug molecules. To date, CD polymers have been intensively studied in pharmaceutics, including the delivery of anti-cancer drugs [5], and demonstrated controlled drug release, limited toxicity, and a good pharmacokinetic profile leading to prolonged exposure to the drug. Thus, we suppose that this hybrid cyclodextrin-polymer technology could be considered as an advanced smart system for drug delivery of temoporfin. In the present work, we demonstrated efficient encapsulation of mTHPC in epichlorohydrin-crosslinked CD polymers based on β-CD (βCDp) and carboxymethyl-β-CD (CMβCDp) monomers. The estimated binding constants were $K = 2.5\times10^6 \pm 4.9\times10^4\ M^{-1}$ and $K = 7.1\times10^5 \pm 3.8\times10^4\ M^{-1}$ for βCDp and CMβCDp, respectively. We showed slower drug release from CD polymers compared to monomeric CD upon the dilution in PBS. *In vitro* experiments demonstrated strong dependence on cellular uptake of mTHPC in human pharynx squamous cell carcinoma (FaDu) *in vitro* models (2D monolayer cells and 3D multicellular spheroids) on the CD polymer concentration. Despite their size (50 nm), CD polymers provide a unique opportunity to increase the penetration of mTHPC into the 3D spheroids at the cost of cellular uptake. We confirm the critical role of affinity constants in the CD-mediated delivery of mTHPC in 3D tumor spheroids. This study suggests that CD nanosponge is a strong candidate for *in vivo* study in preclinical models due to its nontoxicity, potentially prolong the mTHPC in plasma and perhaps improved biodistribution profile compared to CD monomers.

References

1. Stella V.J., He Q. Cyclodextrins // Toxicol. Pathol. 2008. Vol. 36, P. 30–42.
2. Yakavets I., Lassalle H.-P., Yankovsky I., et al. Evaluation of temoporfin affinity to β-cyclodextrins // J. Photochem. Photobiol. A. 2018. Vol. 367. P. 13–21.
3. Yakavets I. et al. The alteration of temoporfin distribution // Int. J. Pharm. 2017. Vol. 529, P. 568–575.
4. Yankovsky I., Bastien E., Yakavets I., et al. Inclusion complexation with β-cyclodextrin derivatives alters biodistribution // Eur. J. Pharm. Sci. 2016. Vol. 91. P. 172–182.
5. Swaminathan S. et al. Cyclodextrin-based nanosponges // WIREs Nanomed. 2016. Vol. 8, P. 579–601.