

# Abstrakt

Polymer-based drug delivery systems represent one of the promising strategies for successful tumor treatment. Conjugation of a low-molecular-weight drug to a synthetic polymer carrier enables targeted drug delivery to tumor tissue/cells and limited systemic toxicity of the drug. The conjugates show extended circulation time, and preferentially accumulate in tumor tissue due to the Enhanced Permeability and Retention (EPR) effect. The EPR effect depends on a structural anomaly in tumor neovasculature, and vasodilators were shown to enhance the EPR effect via an increase of blood supply in the tumor. Polymer drug carriers based on water-soluble *N*-(2-hydroxypropyl)methacrylamide (HPMA) benefit from variable architecture, drug loading and controlled release. HPMA-based conjugates with cancerostatics have already proved high anti-tumor activity, inducing complete tumor regression followed by resistance to a second tumor challenge in experimental murine models.

Three HPMA-based conjugates with organic nitrates (labeled 1, 2, and 3) were prepared as polymer donors of nitric oxide (NO) with the aim to intensify the EPR effect, thereby enhancing accumulation of co-administered macromolecular cancerostatics in the tumor.

In this study, the conjugates were non-toxic to cancer cells and did not potentiate the cytostatic effect of cancerostatics *in vitro*. In mice, conjugates 1 and 2 showed considerably low systemic toxicity. Conjugate 1 enhanced the EPR effect, as it significantly increased doxorubicin (Dox) content in the EL4 lymphoma tumors following Dox delivery by high-molecular-weight polymer carrier, in comparison with the administration of the Dox-conjugate only. In the EL4 lymphoma model, treatment with the star HPMA-Dox conjugate together with conjugate 1 or 2 resulted in a significantly improved outcome. However, conjugate 1 did not improve the treatment of difficult-to-treat 4T1 breast carcinoma. Conjugate 1 also showed a certain capacity in regulation of anti-tumor immune response, as it could modulate expression of CD40 on murine bone marrow-derived dendritic cells *in vitro*.

**Keywords:** *N*-(2-hydroxypropyl)methacrylamide, HPMA, Targeted Tumor Therapy, Polymer Drug Delivery Systems, EPR Effect, Solid Tumor, Organic Nitrates, Nitric Oxide, Nitric Oxide Donors