2. Summary of the PhD. Thesis

Introduction

The use of synthetic polymer carriers of anticancer drugs represents a promising approach to cancer therapy. Conjugation of cytotoxic drugs with polymers may reduce their toxicity and immunogenicity, eliminate undesirable body interactions, improve their solubility, bioavailability and stability (enzymatic, thermal, etc.), and prolong blood clearance. Moreover, polymer drug carriers may enable specific delivery to the diseased tissue and controlled drug release in therapeutically active form. Since the first papers were published in the late 1970's the concept of polymer drug carrier systems has been generally accepted.

In principle basic water-soluble polymer drug delivery systems consist of three parts: of polymer carrier, biodegradable spacer and drug. Preferably, drugs are covalently bound to the polymers via spacers, which enable controlled release of active drug in the target tissue or cells. Probably, most of the studied polymer carriers of cancerostatic drugs have been designed as lysosomotropic systems, where the drug could be released by enzymes in lysosomes of tumour cells. In recent years pH-triggered hydrolytic drug release has been intensively studied. Here, the presence of enzymes is not essential, as the drug might be released in endosomes in tumour cells by the pH decrease from 7.4 (pH of blood) to 5 – 6 (pH in endosomes). For example, the hydrazone bond or *cis*-aconityl group have been employed as pH-sensitive hydrolytically degradable linkages between drug and polymer carrier.

Moreover, the concept of polymer drug carriers enables attachment of other important molecules to the polymer backbone. Thus antibodies, peptides, or other moieties enabling specific interaction with tumour cells receptors could be used as tumour-targeting devices. Nevertheless, it was shown that even polymers without any targeting moieties are "passively" accumulated in solid tumours. This phenomenon, based on differences between properties of healthy and malignant tissue, is called the EPR (enhanced permeability and retention) effect. In general, macromolecules in contrast to low-molecular-weight compounds can pass only partially through the capillary walls of blood vessels of normal tissue and their excess can be removed by lymphatic drainage. The endothelial layer of the vascular capillaries in the tumour tissue is fenestrated and leaky so that macromolecules could extravasate much more easily inside the malignant tissue.

Moreover, the tumour lymphatic drainage system is mostly defective or even missing and thus not capable of draining away macromolecular substances; therefore, macromolecules are retained in tumours. The extent of passive accumulation of macromolecules in solid tumours strongly depends on their size and molecular weight. The EPR effect was observed for copolymers based on *N*-(2-hydroxypropyl)methacrylamide (HPMA) with molecular weights higher than $2 \cdot 10^4$ and grew with increasing molecular weight of polymers. Probably most polymer drug carriers are synthetic polymers with non-biodegradable main chains. These polymers with molecular weight higher than the limit of renal filtration (approx. $5 \cdot 10^4$ for HPMA copolymers) cannot be eliminated from the body with urine and undesired long-term accumulation of carriers can occur in the body. Hence, high-molecular-weight polymer drug carriers exhibiting a significant EPR effect have to contain biodegradable linkages within polymer chains in order to increase passive targeting and to allow renal elimination of the carrier from the body after fulfilling its function. The size of carriers, i.e. molecular weight, could also be increased by using micellar structures formed by self-assembly of polymers with molecular weight lower than the limit of renal filtration.