

7 Summary

Influence of surface-modifying surfactants on the pharmacokinetic behaviour of PMMA-nanoparticles in tumor bearing mice

The aim of the study was to evaluate the influence of surfactants adsorbed onto PMMA-nanoparticles on their surface properties and the enrichment in different tumors.

Polymethylmethacrylat-(PMMA)-nanoparticles produced by gamma irradiation were coated with three different surfactants (polysorbat 80, poloxamer 407, poloxamin 908). The influence of the surfactants on certain characteristics of the particles was investigated *in vitro* and *in vivo* and was compared to the uncoated particles.

In the first part of the investigations the particles were characterized physico-chemically. The size of the particles in distilled water and after incubation in plasma was determined to obtain information on the feasibility of an i.v. administration. There was a clear reduction of particle aggregation indicated by a reduced size after the addition of surfactants in comparison to the uncoated formulation.

The particles, that were coated with surfactants were stable over 3 days without any significant change of particle size distribution. The results of the stability investigations were confirmed by the zeta-potential measurements. The coated particles showed a reduction of the zeta-potential in comparison to the uncoated group. The size of the particle diameter measured by laser light diffraction was in the same range as detected by electron microscopy.

The patterns of the protein adsorption onto the different particles was estimated in human serum and plasma with the 2-D-gel electrophoresis.

In the second part of the investigations the body distribution of the four particle batches was detected in three different tumor models.

- In a murine melanoma model a maximum concentration of 14,5% and 15,6 %, respectively, of the administered dose of poloxamer 407 and poloxamine 908 coated particles was found in the tumor at two hours after injection.
- A much lower enrichment (<1%) of particles in the tumor was found using a breast cancer xenograft model.
- For the third trial it was necessary to develop a glioblastoma-model in order to consider the special conditions of the blood-brain-tumor-barrier. Therefore, an intracerebral growth

of the tumor cells was essential. With none of the particle formulations a higher concentration in the tumor-bearing than in the tumor-free brain hemisphere was obtained. In all three trials only for the poloxamer 407 and the poloxamine 908 coated particles a prolonged circulation and high blood concentration was found. The investigations performed to characterize the neoangiogenesis in the three tumor models used showed a very different VEGF- and FLK-1-expression. It seemed that the altitude of the particle concentration in the tumorous tissue depended on the degree of the tumor-induced blood vessels. None of the studied *in vitro*-properties correctly predicted the behaviour of the particles *in vivo*. In the future it will be necessary to look for more suitable features to correlate the physicochemical properties of colloidal systems with their body distribution.. Furthermore, it seems to be necessary to use a more individual tumor- and patient-adapted therapy, because of the different particle concentrations in different tumors of the performed experiments.