7 Summary and Conclusion

Local drug delivery generally has the advantage that the systemic drug exposure of the organism remains low. This is above all important when high plasma levels of a toxic agent would result in substantial adverse effects. An example for this is the inhibition of restenosis with antiproliferative drugs after balloon dilatation of the coronary arteries. Inhibition of restenosis has been achieved so far by drug eluting stents which are available on the market. Alternative ways of administering the cytostatic agent paclitaxel selectively to coronary vessels walls have been searched for, because stents cannot always be implanted and healing following stent implantation is delayed due to the increased drug concentration close to stent struts which inhibits cell proliferation. Delayed healing, though, means a higher risk of a sudden thrombotic occlusion followed by infarction and sudden cardiac death since thrombogenic metallic stent struts are not covered by endothelial cells.

The balloons required for vascular dilatation were most effectively coated by dipping them into a solution of the drug in a rapidly volatile organic solvent in folded state: Dosages up to several µg / mm² balloon surface were achieved; the doses on the balloons could be increased by repeating the dip after drying. It was, however, slightly unevenly applied on the balloons and showed quite a high variance between identically treated balloons. The drug adhered well to the balloons. The coating of the already folded balloons carries the advantage that there is no risk to damage the applied layer by subsequent folding. The attempt to examine the doses applied to the balloon in a non-destructive way by measuring fluorescence of an added fluorescent dye did not succeed.

Water solubility of paclitaxel is too low (ca.10 µM) for the local administration in arteries to prevent neointimal proliferation. The solubility in the angiographic contrast media is clearly better (ca. 50 µM) but still higher concentrations are desirable, because the contact time between the contrast medium and the vessel is very short. By mixing the X-ray contrast media with a small portion of highly concentrated paclitaxel solution in ethanol it was possible to produce 200 µM supersaturated drug-contrast media-preparations, which were stable for at least 24 hours and applicable during the cardiac intervention. The concentrated solution of the drug in ethanol to be

added to the contrast medium was portioned into 1 ml syringes. An anhydrous, slightly acidic solution proved to be sufficiently stable. The content of the syringe is rapidly injected into the contrast medium bottle, which is sealed by a rubber stopper, immediately before use and mixed inside the closed bottle. Together with its carrier, the drug is injected selectively into the coronary vessel by an angiographic catheter, and due to its high lipophilicity, rapidly taken up by the vessel wall. By using photon correlation spectroscopy no micelle formations could be found in the contrast media. Presumably interactions between the lipophilic drug and the aromatic contrast medium molecules are causing the increase in solubility without the formation of larger aggregates.

Colloidal iron oxide solutions as they are used as contrast media in magnetic resonance imaging are accumulating in atherosclerotic plaques. If loaded with paclitaxel they could serve as carrier for targeted therapy. The loading by simple adsorption succeeded only inadequately. Thus, further studies applying different methods, would be desirable.

Local drug delivery to prevent restenosis after balloon dilatation or stent implantation is possible and useful, because it can cause systematic adverse effects to be avoided. Alternative techniques to the commercially available drug eluting stents could currently be the application of paclitaxel using coated balloon catheters or supersaturated solutions in the already used contrast media. Studies presented in this dissertation suggest that, in both, very different and unusual methods of application, acceptable pharmaceutical preparations can be found, although innovative solutions to a variety of problems will be required. The potential of using magnetite-colloids as carriers, however, will need more experiments to achieve an effective drug loading.