Aim of thesis

The principles of dialysis have been known as far back as the late 19th century. One of the earliest reports of dialysis being used to monitor specific compounds in mammalian tissues is from 1954, with corticosteroids being isolated from human blood samples and beef adrenal homogenate (Axelrod and Zaffaroni, 1954). The use of microdialysis for *in vivo* sampling was first reported in 1972 (Delgado, DeFeurdi et al., 1972), when a small dialysis probe was implanted intracerebrally in monkeys, combined with an electrode for stimulation. In rats, the use of microdialysis was first reported in 1982 and 1983 (Ungerstedt, Herrera-Marschitz et al., 1982; Hernandez, Paez et al., 1983), also with intracranial implantation of a microdialysis probe. Originally the *in vivo* dialysis method was limited to neurological studies, monitoring endogenous compounds. From 1988 onwards, *in vivo* microdialysis studies were also carried out in other tissues, such as blood, fat and muscle (Arner, Bolinder et al., 1988; Hallström, Carlsson et al., 1989). The use of *in vivo* microdialysis to study exogenous compounds was first reported in 1990, when the concentration of theophylline in the rat was described in relation to behavior changes after subcutaneous injection of theophylline (Ståhle, Segersvärd et al., 1990). Since then, microdialysis has been increasingly used to determine absolute concentrations in a variety of tissues, both in the pharmaceutical industry (Mathy, Preat et al., 2001), and in clinical settings (Müller, 2000). However, as microdialysis has been more widely used for pharmacokinetic applications, problems have arisen with lipophilic compounds, which adhere to the materials used, resulting in low observed recoveries and poor time resolution (Carneheim and Ståhle, 1991). For any sampling method to be applicable for pharmacokinetic studies however, the recovery must be high enough to obtain sample concentrations above the lower limit of quantification, and the response time must be quick enough to monitor rapid concentration changes.

In the literature so far, the characterization of microdialysis probes has been limited to the description of the recovery, or at best of the mass transfer coefficient K of the probes used (Sun and Stenken, 2003). No attempts have been made to further define the responsiveness of a probe to concentration changes, even though this is a vital criterion for the suitability of microdialysis for pharmacokinetic applications.

The aim therefore of this dissertation is to establish a well defined approach to test and describe the responsiveness of microdialysis materials (tubes and probes) to concentration changes, and to quantify the adherence of the dialyzed compound to these materials. Then, applying this approach to a model lipophilic compound, the aim is to select suitable materials for the microdialysis of such 'sticky' compounds. This work will thus provide an important step towards the validation of the microdialysis method for pharmacokinetic applications *in vivo*.