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Preface

Local controlled drug delivery to the brain

The treatment of brain diseases is particularly difficult due to the Blood Brain Barrier (BBB). Generally, only low molecular mass lipid-soluble molecules and a few peptides and nutrients can cross this barrier to a significant extent, either by passive diffusion or using specific transport mechanisms. Thus, for most drugs it is difficult to achieve therapeutic levels within the brain tissue. In addition, highly potent drugs (e.g. anticancer drugs and neurotrophic factors) that may be necessary to be delivered to the Central Nervous System (CNS), often cause serious side effects when administered systemically. An interesting possibility to overcome these restrictions is to administer the drug directly into the brain tissue (intracranially). However, the risk of CNS infections is considerable with this administration route. To reduce the administration frequency (ideally to one single application) controlled delivery systems can be used which release the drug in a pre-programmed, desired manner over prolonged periods of time (days to months). The drug can for example be embedded within a biocompatible matrix former and different processes (e.g. dissolution, diffusion and degradation) can be involved in the control of the resulting release kinetics. Biodegradable matrix formers offer the important advantage to avoid the removal of empty remnants upon drug exhaust.

Different types of CNS diseases can be treated with such intracranially administered, biodegradable controlled drug delivery systems, including brain tumors and neurodegenerative disorders (e.g. Parkinson's and Huntington's disease). The efficiency of a variety of devices has been demonstrated in vitro as well as in vivo (animal studies and clinical trials). Gliadel® was the first (and is still the only) pharmaceutical product available on the market which is based on the principle of intracranial controlled drug delivery. It is a disc-shaped wafer, consisting of the anticancer drug BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea; carmustine] and the biodegradable matrix former poly[bis(*p*-carboxyphenoxy)] propane:sebacic acid (PCPP:SA). In 1996, Gliadel® got approved by the Food and Drug Administration (FDA) for the treatment of recurrent glioblastoma multiforme. This was the first time in 23 years that the FDA approved a new treatment for malignant gliomas.

The European Commission supported a Research and Technological Development Project (BCDDS: Biodegradable Controlled Drug Delivery Systems for the Treatment of Brain Diseases; Contract No. QLK3-CT-2001-02226), in which six university laboratories and one pharmaceutical company were involved (the groups of Prof. J.P. Benoit at the University of Angers, Prof. P. Brundin at the University of Lund, Prof. A.T. Florence at the University of London, Prof. A. Göpferich at the University of Regensburg, Prof. P. Menei at the University of Angers, Dr. J. Richard at Mainelab, and Prof. J. Siepmann at the Free University of Berlin/University of Lille). The major objective of this project was to develop novel and improved therapeutic strategies based on biodegradable controlled drug delivery systems to restore, maintain and improve cell, tissue and organ functions in the CNS. Parts of the scientific outcome of this collaboration are presented in this special issue.

First, overviews are given on the current state of the art of local controlled drug delivery to the brain. Despite of the considerable practical benefits of this type of advanced treatment methods, only little is yet known on the underlying mass transport mechanisms controlling drug release out of the pharmaceutical dosage forms and the subsequent drug transport through the living brain tissue. This can be attributed to the complexity of the involved physical, biological and chemical phenomena. Many factors, including the properties of the drug, composition and geometry of the delivery system as well as anatomic characteristics of the healthy/pathologic brain tissue strongly affect the resulting drug release kinetics and subsequent distribution within the CNS. Thus, the design of biodegradable intracranial controlled drug delivery systems is particularly challenging.

In the second part, emphasis is laid on novel lipid-based controlled drug delivery systems, especially triglyceride-based implants. Different types of drugs, including proteins, have been incorporated in such systems and their performance measured in vitro as well as in vivo. This type of dosage forms can be expected to be particularly promising for drugs that cannot be encapsulated into polyester [e.g. poly(lactic-co-glycolic acid) (PLGA)]- or polyanhydride-based matrices. The latter are currently the most frequently used excipients to control drug release from parenteral dosage forms. However, upon degradation of these polymers, acids are generated which can lead to significant drops in the micro pH within the delivery system and, thus, to the potential loss of the activity of the incorporated drug (e.g. protein). The spectrum of drug release patterns that can be provided with these alternative, lipid-based dosage forms has been studied as well as their biocompatibility and in vivo erosion behavior.

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In the third part, different types of poly(lactic-co-glycolic acid) (PLGA)-based microparticles aimed to treat brain diseases are presented and their in vitro as well as in vivo performance reported. Special emphasis is laid on a better understanding of the underlying mass transport mechanisms in these systems. In particular, the potential occurrence and importance of autocatalytic effects is pointed out. Significant drops in the micro pH within the dosage forms cannot only affect drug stability but also the degradation behavior of the matrix former (the hydrolysis of esters being catalyzed by protons). The importance of key formulation parameters (including the microparticle size and porosity) for the underlying mass transport mechanisms and resulting drug release kinetics has been quantified and explained.

One of the long term goals of this special volume is to show how biodegradable controlled drug delivery systems can improve the efficiency and safety of various types of pharmaco therapies for brain diseases.

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