CHAPTER 8

Concluding remarks and future perspectives

CONCLUDING REMARKS

Over the past decades there has been a growing interest in the development of biopharmaceuticals as inhalation products, not only to obtain a local therapeutic effects but also to obtain a systemic absorption. As a consequence, pulmonary drug administration is nowadays connected to various therapeutic treatment modalities. Drug inhalation is no longer solely applied for treatment of local lung diseases, but its scope has widened to treat systemic diseases, to evoke a systemic effect without systemic absorption (e.g. vaccination) or to obtain systemic and local levels to treat for instance tuberculosis or cystic fibrosis.
Those biopharmaceuticals that are suited for inhalation can be formulated as a liquid, that is aerosolized by means of auxiliary energy at administration, or, they can be formulated as a powder for inhalation which is aerosolized upon inhalation by utilizing the patients' inspiratory force. Dry powder inhalation is the preferred means of administration for most patients as electricity or pressurized air are not needed. In addition, the short administration time, the better stability of the powder compared to a liquid formulation, the higher lung deposition, the more robust and reliable inhalation mode and size of the administration device are also advantageous..

In this thesis, we successfully formulated a number of biopharmaceuticals, each with different physico-chemical properties, as a dry powder for inhalation. Depending on the physical properties of the biopharmaceutical (e.g. stability, solubility, pK_a, molecular weight) a certain formulation strategy can be chosen. Relatively stable (small) peptides, such as cetrorelix or cyclosporine A, can be formulated as a powder for inhalation by using standard milling techniques and formulation as adhesive mixture or spherical pellet. More complex manufacturing processes and/or formulations may be needed when the biopharmaceutical is sensitive to chemical or physical degradation (e.g. rhDNase). So far the preferred manufacturing process seems to be spray drying because it is (next to freeze drying) the single process that has been successfully employed in commercial scale manufacturing for many years. Consequently, this process is well-known and well-described. A major disadvantage of the common freeze drying process is the fact that the obtained solid material has particulate properties that are unsuitable for inhalation and the material shows poor milling properties (e.g. high

tendency to stick to the walls of the equipment, moisture sensitivity, high tendency for crystallization). All other manufacturing processes (like spray freeze drying or supercritical drying) need further development and scale up and they are therefore expected to be more expensive. To protect chemically and/or physically sensitive biopharmaceuticals, we have demonstrated the versatility of sugar glass technology. Of the currently available excipients that can be used in sugar glass technology, inulin seems one of the best materials to meet stability demands: its high glass transition temperature allows storage at room temperature while the amorphous state is maintained. Other excipients, such as trehalose or sucrose tend to collapse at ambient conditions rendering them useless as inhalation products. Moreover, sugar glass technology in combination with spray (freeze) drying can be used for particle design. Particle size, shape and density can be designed to render material that in combination with the chosen inhaler provides the best possible aerosol. In addition, with sugar glass technology, the dissolution rate of poorly soluble active ingredients can be improved, which may improve their bioavailability.

Efficacy and safety research in animals are a relevant part of the pre-clinical development program of new drug products. For inhalation products it is almost impossible to mimic the pulmonary drug administration in humans. First, significant differences exist between man and animal regarding lung anatomy and breathing profile. Second, spontaneous inhalation through an inhaler is only rarely performed by most animals. Two powders for inhalation were tested in mice or rats, for which two different administration methods were used. The administration method of dry powder in mice was an aerosol chamber. The powder was aerosolized into the chamber by creating an inspiratory air flow through an inhaler. Mice were put in restrainers and attached to the aerosol chamber such that only their nose was exposed to the aerosol. The amount the mice inhaled depended on the aerosol concentration in the chamber and duration of exposure. With this model, different aerosol properties may be investigated when coupled with an appropriate method to determine deposition. The method used for aerosol administration to rats was intratracheal administration with the PennCentury insufflator. With the insufflator, aerosol properties are of less importance, yet accurate doses can be administered, which makes this method suitable for experiments where accurate dose administration is needed. Both

methods, nose-only exposure and insufflation, are complementary and considered essential models for inhalation product development.

FUTURE PERSPECTIVES

Biopharmaceuticals that will be evaluated as inhalation products should possess a true therapeutic advantage. When the only reason to develop an inhalation product is that it is "a more comfortable route of administration than the injection" the chances of market success are limited as was shown by the Exubera® case. Only in those cases where pulmonary administration offers a true therapeutic advantage, such as an increased efficacy or an improved safety, pulmonary biopharmaceuticals may become successful. Typical examples of such biopharmaceuticals are:

- biopharmaceuticals that can be used to treat local lung disease,
- biopharmaceuticals that evoke the best systemic therapeutic response after inhalation (e.g. vaccination), or
- biopharmaceuticals that cause serious side effects when administered via another route (e.g. injection)
- biopharmaceuticals that require rapid absorption, but for any reason cannot be injected (e.g. for hygienic reasons)

For each biopharmaceutical suited for inhalation a taylor-made manufacturing process and formulation is to be designed that meets general requirements, such as the pharmaceutical aspects as well as aspects related to efficacy, safety, patient compliance and health care costs. The technology to develop and manufacture biopharmaceuticals as powders for inhalation is nowadays available although the application of the technology is still rather limited.

One of the major research topics that may enable a broader use of this technology in the future is the understanding of the processes that occur during particle formation. With this knowledge, particles that are easily dispersible and demonstrate excellent deposition characteristics can be prepared. Drug product and administration device should be regarded as a single entity since not all formulations will be optimally aerosolized with just one inhaler; i.e. the best possible inhaler will not be suitable for all different formulations. The optimal result can only be reached when formulation and inhaler are optimized regarding the specific characteristics and interactions they have. Furthermore, computational

fluid dynamics and computational particle tracking will receive more attention in the inhalation field, since these technologies can speed up product development, both by indicating the optimal starting point for a development based on *in silico* simulations as well as through the generation of additional information on deviating performance during development.

Further refinement in animal models for pulmonary drug products is also anticipated but also urgently required. To appropriately test inhalation drug products, improved animal models are needed since the use of animal models is a prerequisite to substantiate the marketing authorization dossier. These models should be able to discriminate between different drug products in terms of aerosol behaviour and subsequent pharmacokinetics and –dynamics. In addition, the deposition characteristics would need to be analyzed. Improvements in methods to determine the deposition characteristics in laboratory animals are possible, for example by *in vivo* bioluminescence or fluorescence.

Safety of biopharmaceuticals is a key aspect as protein structures may change as a consequence of purification, production, storage or even use. Such changes may lead to unwanted immunological responses, even when patients are immune tolerant to the endogeneous protein. As at present the exact role of an altered protein structure is unknown, biopharmaceuticals are likely to be subjected to rigorous immunological profiling in animal studies, but also in humans.

Finally, many research efforts will be fuelled by various societal aspects related to the current state of the pharmaceutical industry and policies around it. The declining success of pharmaceutical research is emptying the industry's pipelines; this will result in fewer new drug products that enter the market. Those products that are promising should be brought to the market as fast as possible and in the end in the most optimal way possible, in order to cover for losses of unsuccessful development projects.
Tighter requirements from regulatory authorities address society's requirement for more efficient and safer medicines, preferably provided at lower costs. However, since safety and efficacy can only be improved through extensive research and optimized drug administration, possible

future cost savings can only be generated through significant investments in today's pharmaceutical research and development.

To conclude, this thesis demonstrates that many manufacturing processes and formulations are already available to design tomorrow's biopharmaceutical drugs as inhalation products.