In this thesis, studies on the treatment of CF patients with antibiotic containing aerosols are described. After an overview of the history of cystic fibrosis related to inhalation therapy in chapter 1, chapter 2 deals with the first European consensus on inhaled medication and inhalation devices in CF. This document describes the current knowledge on treatment with inhaled drugs (among which are antimicrobial agents). Next to the drugs currently in use and new drug therapies in development, the fundamentals of inhalation in CF treatment and practical aspects of inhalation of drugs (e.g. compatibility of mixtures and cleaning) are described. This comprehensive review incorporates the fact that several new drugs, drug formulations and new inhalation devices have been developed and have been marketed recently. The consensus is intended as a reference document which may form the basis for an improved understanding of inhalation treatment in CF by clinicians, pharmacists and other health care professionals and for further research activities.

In chapter 3, the focus is on the administration of tobramycin for inhalation (TOBI®), using an identical nebuliser with two different compressors in CF patients. Although the manufacturer of TOBI® has recommended a specific nebuliser and compressor for drug administration, many patients use another combination for inhalation. The choice for a nebulising device is often determined by the device that is already present at home for use with other drugs or by the reimbursement policy of the health insurance company. This may result in variation of the delivered dose and lung deposition compared to the reference combination and is likely to influence treatment effects. For example, using a compressor with higher flow results in smaller particles and a shorter nebulisation time. This may not only increase therapeutic efficacy but also induce a higher risk on adverse effects due to a higher (peripheral) lung deposition. In chapter 3 it was concluded that both compressors, the PortaNeb® and the CR60®, attached to the PARI LC PLUS® nebuliser, can be used to nebulise tobramycin solution for inhalation, but with the restriction that a higher risk on adverse effects or toxicity with the CR60® has not been fully explored. On the other hand, an increased therapeutic efficacy would be a major advantage. Both clinical effects should be subject for a future study.

This example of differences between compressors underlines the importance of studying each nebulising device with a drug formulation for inhalation in a clinical situation in CF. This requirement has been adopted by the European consensus on inhaled medication and inhalation devices in CF (chapter 2) and is also incorporated in the EMEA Guideline on the pharmaceutical quality of products for inhalation and nasal products, which states that ‘for products for nebulisation the nebuliser system(s) and settings that were proven to be effective and safe in vivo must be indicated, including information on the droplet size distribution, drug delivery rate and total drug delivered’.

Colistin is a polypeptide antibiotic that is most potent in its colistin free base form. However, currently the sulfomethate salt, which needs hydrolisation to become active, is routinely administered. More activity per milligram of drug is an advantage in dry powder inhalation,
as, theoretically, less powder mass per inhalation is needed to obtain a comparable clinical
effect to a reference treatment (in this case wet nebulisation). This favours colistin sulfate over
colistimethate sodium, which is a prodrug that is converted \textit{in vivo} into several metabolites and
colistin. The first explorations on a colistin dry powder inhaler were done with colistin sulfate,
but a subsequent study, described in \textit{chapter 4}, demonstrated that colistin sulfate is not suit-
able for inhalation in CF patients due to its irritating effects. As a consequence, colistimethate
sodium was designated as the chemical form of choice, resulting in a larger dry powder mass
per dose, based on colistin activity per mg of dry powder mass.

In \textit{chapter 5}, the development of a disposable dry powder inhaler (Twincer\textsuperscript{®}) for high pow-
der doses is described. The development process of a dry powder inhaler is influenced by drug-,
device- and patient-bound parameters. It is the combination of these parameters that deter-
mines the success of the inhaler. This chapter focuses on the design and \textit{in vitro} results of this
inhaler loaded with a colistimethate sodium dry powder mixture. It was shown that the inhaler
is able to produce high fine particle fractions as a result of an extremely high de-agglomeration
efficiency and with a total inhaler accumulation of only 5-6% at 4kPa (approx. 67 L/min). Its
simple design, the fact that it is for single use (disposable), the good moisture protection of the
drug formulation in a blister and low production costs make this inhaler suitable for applica-
tions in CF treatment but also for other aerosolized drugs for local or systemic use.

After having determined that colistimethate sodium is the colistin-salt of choice for inhala-
tion in CF-patients, a bench study showed that effective dispersion of colistimethate sodium
in a dose up to 25 mg in the newly designed Twincer\textsuperscript{®} dry powder inhaler can be obtained,
resulting in particles (volume median diameter) with a $X_{10}$, $X_{50}$ and $X_{90}$ of 0.7 μm, 1.6 μm, 3.1 μm
\textit{(chapter 7)} and 0.9 μm, 2.1 μm and 3.8 μm \textit{(chapter 8)} respectively, using dry powder mixtures
with different primary size distributions, measured by laser diffraction analysis and favourable
for peripheral deposition in the lung. The obtained fine particle fraction varied from 43.8% at
34 l/min (1 kPa) to 50.6% at 67 l/min (4 kPa) which indicates that the size distribution of the
emitted aerosol is comparable at different inspiratory flows \textit{(chapter 7)}.

These results show that the multiple air classifier technique, applied in the Twincer\textsuperscript{®} inhaler,
is a highly effective de-agglomeration principle that enables patients to inhale a high drug
dose as a dry powder aerosol with a high fine particle fraction at a relatively low inspiratory
effort. A lower inspiratory flow reduces oropharyngeal and upper respiratory tract deposition
and increases deposition deeper in the lung.

Inhalation with this colistimethate sodium dry powder inhaler with the Twincer\textsuperscript{®} inhaler in
pilot studies by small groups of healthy volunteers and cystic fibrosis patients \textit{(chapters 6, 7,
8)} resulted in highly variable $C_{\text{max}}$ and AUC-values, which is not surprising as inter-patient vari-
ability in CF patients is well known. Comparison of inhalation with the colistimethate sodium
dry powder inhaler to nebulisation with the nebuliser-compressor in CF patients resulted in a
140% and 270\% \textit{(chapter 7)} or 140\% and 300\% \textit{(chapter 8)} higher relative lung dose based
on actual dose and nominal dose respectively. However, absolute values of $C_{\text{max}}$ and AUC after
25 mg colistimethate sodium dry powder were lower compared to the 158 mg colistimethate sodium solution. Based on these results, a dry powder dose of approximately 50 mg has been estimated to result in a similar bioavailability (serum levels) compared to (jet) nebulisation (data not shown). The volunteer study (chapter 6) showed that no detectable serum levels were found after oral ingestion of 80 mg of colistimethate sodium and therefore all colistin serum level measurements can be attributed to systemic absorption following inhalation.

These consistent results show that dry powder inhalation of colistimethate sodium with the Twincer® inhaler is more efficient than wet nebulisation of the same drug using a Ventstream®-PortaNeb® inhaler/compressor combination. Moreover, treatment with the Twincer® is less time consuming compared to (jet) nebulisation (approximately less than one minute per dose versus 30 minutes). Finally, the use of a disposable dry powder inhaler is safer from a microbiological perspective.

Based on these findings, clinical studies on optimising the amount of drug that can be inhaled in one manoeuvre with the Twincer® accompanied with studying peripheral deposition after inhalation are advocated.

Furthermore, although the optimal (lung) dose of colistimethate sodium or tobramycin is not known, peripheral deposition studies with a focus on clinical efficacy will hopefully help to find an answer to the question what dose should be put in which inhaler used by which patient to obtain a maximal clinical response with minimal toxicity.

The results from chapters 6, 7 and 8 also show that differences between nominal and actual inhaled doses (particle mass) in jet nebulisation are large: a large fraction of the dose stays behind in the nebuliser cup. This observation stresses the importance of determining the actual dose (output) in inhalation studies, as it provides information on the amount of drug that can be made available for inhalation. This information is especially informative in jet nebulisation studies, as jet nebulisers are known for their dose release inefficiency.

From the above it may be obvious that many parameters determine research outcomes in CF inhalation research, predominantly guided by limitations because of lack of fundamental knowledge of the inhalation of drugs in CF. With clinical efficacy as a starting point and central objective at the same time, continuing scientific efforts are needed to improve inhalation therapy for CF patients in future.