Inhalation is a convenient way to deliver drugs to the respiratory tract in the treatment of respiratory diseases. Different types of devices, such as pressurised metered dose inhalers (p-MDI’s), nebulizers or dry powder inhalers (DPI’s) are used for the pulmonary delivery of drugs. The present thesis focuses on dry powder inhalation. Inhalation technology of inhalation therapy with DPI’s is not just the administration of powder to the patient, resulting in a clinical effect. Many variables are involved in the steps between powder formulation and clinical effect. The unique combination of research groups in this multidisciplinary project enabled investigation of variables involved in inhalation, from different points of view. This thesis is divided in two major experimental parts.

**Part one** of this thesis deals with the technical and physiological aspects of dry powder inhalations. The aim of this section is to investigate the effects of inhalation performances on the output of fine particles from DPI.

In *chapter 2* the effect of inhalation through a resistance to airflow on the inspiratory flow curve is described. For DPI’s the principle of operation is to use the patient-generated inspiratory flow as energy source for emptying of the dose system and the delivery of fine particles into the respiratory tract. Therefore, the inspiratory flow curve is of major importance. The aim of this study is to define the essential parameters for a proper description of the inspiratory flow curve through a resistance to airflow, such as a DPI. The main parameters for a proper description of an inspiratory flow curve are the peak inspiratory flow (PIF), the flow increase rate (FIR) and the inhalation time. It is concluded that the use of a resistance to airflow has a significant impact on the parameters of the inspiratory flow curve. But with the use of resistance to airflow in the design of a DPI, it is also possible to control and manipulate the inspiratory flow profile, performed by the patient, as a potential tool to optimise the performance of the DPI.
In chapter 3 and chapter 4, the relationship between the inspiratory muscle strength and the inspiratory flow curve is investigated in healthy subjects, asthmatics, mild to moderate COPD patients and COLD patients with significantly reduced peak maximal inspiratory pressure (P'MIP). The aim of the study is to determine the relationship between a human performance parameter and the parameters of the inspiratory flow curve. From chapter 3 it is concluded that the P'MIP, as indicator of the inspiratory muscle strength, has a predictive value for the driving pressure for inhalation. Linear relationships are found between the peak inspiratory flow (PIFRx) through a resistances to airflow and the square root of P'MIP. It is also found that increased resistance to airflow results in a reduction of the inter-individual variation in PIFRx over a wide range of P'MIP values. Therefore, the use of a relatively high resistance to airflow in the design of DPI’s is preferred.

In addition, from chapter 4 it is concluded that the strongly reduced P'MIP-values result in a reduction of the generated PIFRx-values, in the group of COLD patients with a P'MIP of less than 6 kPa. However, the generated P'MIP and PIFRx-values in this group are sufficient for adequate use of low as well as high resistance to airflow DPI’s. Although it should be noted that not all patients reach the optimal inspiratory flow rates for the highest disintegration and deposition of the drug particles.

A combined conclusion of chapter 3 and chapter 4 is that the inspiratory flow results obtained in healthy volunteers can be used to predict PIFRx for patients, if the P'MIP-values of these patients are available.

In chapter 5 the training effects of the daily use of a high resistance to airflow DPI’s is investigated in a simulated inhalation therapy. The simulated inhalation therapy consisted of five forceful and deep inhalations, performed twice daily, through a dummy DPI. The aim of the study is to investigate the effect of daily use of a high resistance to airflow DPI, as inspiratory muscle training, on the P'MIP and PIFR. The simulated inhalation therapy results in a significant increase in P'MIP, and therefore in an increase in PIFR. The results of this study might have consequence for clinical trial studies with DPI’s. During this studies the inhalation performance by the patients increased, only caused by the use of an inhaler. This might result in an increase in deposition of inhaled drugs.

In chapter 6, the in vitro results from testing of the performance of four corticosteroid DPI’s are presented. The test conditions are based on previously measured inspiratory flow parameters. In this study the effects of both the PIFRx and the flow increase rate (FIR20-80%) on the fine particle output from the DPI’s are investigated. It is concluded that DPI performance depends on PIFRx as well as the FIR20-80%. Large differences in fine particle output are found for different DPI’s. These differences should be taken into account when changing the prescription of the inhaler device. It is also recommended to patients to inhale forcefully and deeply through the DPI to obtain the highest fine particle output.
In chapter 7, a theoretical explanation and experimental solution of errors in pneumotachograph readings is presented. The errors are found during measurements with an add-on device, as described in chapter 3 and chapter 4. The described theoretical explanation based on physical transport phenomena is in excellent agreement with experimental test results. Recorded inspiratory flow curves are corrected in flow and in inhaled volume according to the described corrections.

Part two of this thesis deals with aspects of prescribing and use of DPI’s. The aim of this section is to provide not only knowledge about the patients’ use of DPI’s but also information about the intervention possibilities for changes in prescribing of inhaled medication.

In chapter 8 the evoked set as applied by chest physicians, general practitioners and pharmacists (prescribing and delivering inhalation devices) was investigated. The aim of this study is to investigate which choice criteria and actual (technical) knowledge about inhaler devices are involved with the prescribing of an inhaler device in the treatment of asthma and COPD. From chapter 8 it is concluded that the choice of an inhaler device is mainly based on a limited number of available devices, the so-called evoked set. The most important patient related criteria for the choice of an inhaler device are handling, and the fact that the new inhaler is the same inhaler as already in use by the patient. The most important technical related criteria are lung deposition and inspiratory flow. In order to evaluate the decision criteria for a particular inhaler device, the knowledge of the chest physicians, general practitioners and pharmacists about inhaler performance should be up to date. It is found that physicians usually prescribe medication habitually and for a number of health care providers the actual knowledge about technical aspects of the prescribed inhaler devices is inadequate.

Chapter 9 provides an overview of inhalation-instructions to patients for commonly used DPI’s. The aim of this study is to connect technical knowledge about DPI’s with an inhalation-instruction. This combined information can be used when inhalation-instruction is given to patients.

In chapter 10 the patient compliance of inhaled corticosteroids is investigated, based on prescription data from pharmacies. The aim of this study is to measure differences in patient compliance related to the used inhaler device and related to the different age categories. For about one third of the patients it is possible to calculate a patient compliance. It is concluded that 47.6% of these patients are likely to underuse their medication. Only 44.7% of these patients have a sufficient patient compliance between 85% and 130% of the prescribed dosage, and 7.7% of these patients are likely to overuse their medication. Patient compliance is age dependent, and the highest percentage of patient compliance is found in elderly
patients. It is also found that with increased age, the (relative) number of patients with a possibility to calculate patient compliance increases. Especially for the maintenance treatment with inhaled corticosteroids, patient compliance is of major concern.

In chapter 11 some **final remarks** and **perspectives** of the presented research projects are given. Aim of this chapter is to merge the research results on dry powder inhalation as investigated from the different perspectives. The different perspectives are the result of the multidisciplinary input of the different research groups. The therapeutic efficacy of the inhalation therapy is determined by a proper delivery of drug particles in the target area, the lungs. Important determinants for this are the used inhaler device, a proper use of the inhaler device by the patient, and a proper compliance to the therapy. Large differences in fine particle output, found for the different inhaler devices, should be taken into account when a prescription for a particular patient is made. On the other hand, results from the studies about aspects of prescribing and use, show that compliance to the therapy can be improved. This can be done by providing adequate inhalation-instructions to the patient and by proper prescribing of inhalation therapy, based on at least some rational decisions concerning technological knowledge about inhaler devices. Lung deposition from the inhaler device in daily use might improve if the patients are well instructed to perform a forceful and deep inhalation through their DPI. This maximal inhalation not only improves the fine particle output, it also improves the reproducibility of the inspiratory flow curve, and under some conditions it might improve patients P·MIP due to a training effect. An increase in technical knowledge by the health care providers, such as chest physicians, general practitioners and pharmacists, may result in making proper decisions when prescribing an inhaler device, as well as providing an adequate inhalation-instruction to the patient.