Chapter 1

Introduction to Inhalation Therapy with Dry Powder Inhalers
1.1 Introduction

The respiratory tract is one of the oldest routes for the administration of drugs. Anaesthetics, aerosolised drugs, smoke or steam have been inhaled for medical purposes for centuries. Over the past decades inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases, such as asthma or COPD\(^1\). Historically, the evolution of inhalation therapy can be traced to India 4000 years ago, where the leaves of the *Atropa Belladonna* plant, containing atropine as bronchodilator, were smoked as a cough suppressant\(^2\). The development of modern inhalation therapy began in the nineteenth-century with the invention of the glass bulb nebulizer. The development of the first pressurised metered-dose inhaler (p-MDI) for asthma therapy in 1956 was a major advance in the use of aerosols for drug delivery to the lungs\(^3\). However, the required hand-lung coordination of the patient and the use of environmentally damaging CFC propellants, are major drawbacks of the traditional p-MDI. Dry powder inhalers (DPI's) were introduced to overcome these drawbacks. From the first introduction of a DPI in 1971 (Spinhaler), several DPI's have been added to the collection of available inhalers. DPI's represent a significant advance in pulmonary delivery technology. They are breath-controlled and so coordination problems have been overcome. DPI's are also potentially suitable for the delivery of a wide range of drugs, such as anti-asthmatics, peptides and proteins. DPI's can also deliver a wide range of doses from 6 µg to more than 20 mg via one short inhalation\(^4,5\). This chapter gives an introduction to inhalation therapy with modern dry powder inhalers, from the anatomy of the airways, mechanics of pulmonary ventilation,
powder formulation, technological aspects of interest for the understanding of DPI design, to the prescription and use of DPIs.

1.2 Aim of this thesis

It is clear that inhalation technology or inhalation therapy with dry powder inhalers is not simply the administration of some powder to the patient which will result in a clinical effect. Many variables are involved in the steps between powder formulation and the clinical effect (figure 1.1). The unique combination of research groups in this multidisciplinary project enabled investigation of variables involved in inhalation, from different perspectives. Relevant inhalation variables include the design (resistance to airflow) of the dry powder inhaler, the patient, and the inhalation-instruction. They represent the whole domain of dry powder inhalation from pharmaceutical technology to inhaler use. Technological and physiological aspects as well as prescribing and use of dry powder inhalers are investigated.

Two main questions are raised. Firstly, the question is raised to what extent the inspiratory muscle function is a determinant for the inspiratory performance through a dry powder inhaler and how this is related to the inhaler performance. Secondly, the question is raised to what extent counselling at prescribing level and patient level can contribute to the correct use of the inhaler device.

Both questions are investigated in different research settings. The first question resulted in a research setting in the University Hospital of Groningen and the asthma centre Beatrixoord, Haren. In this study the relation between the inspiratory flow curve and the inspiratory muscle function was investigated in healthy subjects, asthmatics, Chronic Obstructive Pulmonary Disease (COPD) patients and Chronic Obstructive Lung Disease (COLD) patients with reduced peak maximal inspiratory pressure (P·MIP). Similarities between inspiratory muscle training as applied in COLD patients with reduced P·MIP, and the inhalation through high resistance to airflow DPI’s resulted in an additional study in which the effects of DPI use on the inspiratory muscle strength was investigated.

To answer the second research question, the process underlying the choice of an inhaler device for the treatment of asthma and COPD was investigated. In this study the evoked set for prescribing inhaled medication, as well as the knowledge about the prescribed inhaler devices, was investigated amongst chest physicians, general practitioners, and pharmacists. Adequate knowledge is necessary for proper patient education and counselling. Therefore, an inhalation-instruction was written with technological background regarding the inhaler devices to improve the knowledge by the health care provider about the inhalation technology. The use of dry powder inhalers was measured by calculating patient compliance. Therefore, a database was developed with prescription data concerning the use of inhaled corticosteroids. This database is developed in cooperation with pharmacists from the pharmacists peer review group NODE (Noord-Oostpolder / IJssel-Vecht Delta, the
The research involved in this thesis provides various perspectives concerning the complex interactions between the variables that affect inhalation.

1.3 Asthma and COPD

Asthma is a chronic inflammatory disease of the airways characterised by reversible airway obstruction associated with exacerbations of coughing, wheezing, chest tightness, difficult breathing, and airway hyperresponsiveness. Asthma is predominantly a disease of young individuals\(^6\). Asthma has a high incidence. It is estimated, that over 100 million people worldwide have asthma. Epidemiological studies in The Netherlands have revealed that 10 - 20% of the general population report respiratory symptoms like wheezing and shortness of breath that could indicate the disease asthma\(^7\).

Chronic Obstructive Pulmonary Disease (COPD), which refers primarily to chronic bronchitis and emphysema, is characterised by chronic airway obstruction causing progressive loss of lung function\(^8\). COPD is associated with symptoms of chronic cough and purulent sputum\(^8\). COPD is strongly related to a history of smoking and is predominantly a disease of older patients\(^8\).

Asthma differs from COPD in that there is a greater reversibility, spontaneously and after treatment with bronchodilators or corticosteroids. Some patients with asthma have progressive irreversible airway obstruction and therefore have a form of COPD, and some patients may have coexistent asthma and COPD.

The term Chronic Obstructive Lung Disease (COLD) is used as definition for combined asthma and COPD.

The goal of respiratory therapy is to improve the patient’s quality of live by achieving and maintaining control of symptoms, preventing exacerbations, attaining normal lung function, maintaining normal activity levels, including exercise, and avoiding adverse effects from respiratory medications\(^6, 8\).

1.4 From powder to clinical effect

Applying inhalation therapy in the treatment of pulmonary diseases is a form of targeted drug delivery. It should be appreciated that a very significant improvement in the therapeutic efficacy is achieved when drugs are delivered directly to the site of action in the respiratory tract. The goal of inhalation therapy is to deliver medication directly to the lungs. It is an advantage for the patient if the amount of drug reaching the lungs is maximised and the amount deposited in other regions, like the mouth or oropharyngeal region, is minimised. Reducing the amount of drug that is deposited in the oropharynx can reduce the likelihood of
adverse events\(^9\). The major advantages of inhalation therapy are, rapid onset of the therapeutic effect, lowering of the required dose, compared to systemic administration, and reduction in unwanted side effects.

It is well known that inhalation therapy, especially for asthma and COPD, is very successful even though only a small fraction of the inhaled dose (typically less than 20-30\%) actually reaches the peripheral parts of the respiratory tract. The rest of the dose deposits in the mouth and in the upper airways\(^1\).

The dry powder inhaler device is one of the types of delivery systems that enable generation and delivery of aerosolised drug particles into the respiratory tract. The principle of this therapy is to transfer powdered medication into a clinical effect (figure 1.1). However, the respiratory tract is a strongly branched system, which works excellently as filtering system to avoid penetration of particles into the lungs. To enable penetration into the lungs, the aerodynamic particle size of the inhaled medication has to be small, preferably below 5 to 10 \(\mu\)m, as will be explained in detail in paragraph 1.12. The particle size distribution of the drug is one of the major determinants in drug delivery to the respiratory tract. Special techniques, such as micronisation of drugs in dry powder systems, are required to produce particles (or droplets) in this size range. Because the handling of micronised particles is very difficult, and the amounts of drugs that have to be metered in inhalation therapy are often very low (6 \(\mu\)g to 500 \(\mu\)g), special formulations and devices have to be applied to obtain the required clinical effect from the administered dose.

![Figure 1.1: From powder to clinical effect.](image)

### 1.5 Respiratory system

The human respiratory tract is a branching system of air channels with more than 23 bifurcations from the mouth to the alveoli. This human respiratory tract looks like an inverted tree with a single trunk. The human respiratory system can be divided into four regions, each covering one or more anatomical regions. These regions clearly differ in structure, airflow patterns, function, and sensitivity to deposited particles. The most widely used morphologic model for describing the structures within the lung was initially given by Weibel\(^{5, 10}\) (figure 1.2). The first region is the upper respiratory tract, which includes the nose, mouth and pharynx. The main function of this region is heating and moistening of air. Normal
atmospheric air contains around 40 - 60% moisture and has a temperature of 20 °C. In the mouth, nose and throat the air is heated to 37 °C and moistened till 99% relative humidity.

<table>
<thead>
<tr>
<th>generation</th>
<th>diameter (cm)</th>
<th>length (cm)</th>
<th>number</th>
<th>total cross sectional area (cm²)</th>
<th>Powder deposition by particle diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>trachea</td>
<td>1.80</td>
<td>12.0</td>
<td>1</td>
<td>2.54</td>
<td>7 - 10 µm</td>
</tr>
<tr>
<td>bronchi</td>
<td>1.22</td>
<td>4.8</td>
<td>2</td>
<td>2.33</td>
<td>2 - 10 µm</td>
</tr>
<tr>
<td>bronchioles</td>
<td>0.83</td>
<td>1.9</td>
<td>4</td>
<td>2.13</td>
<td></td>
</tr>
<tr>
<td>terminal bronchioles</td>
<td>0.56</td>
<td>0.8</td>
<td>8</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>bronchioles</td>
<td>0.45</td>
<td>1.3</td>
<td>16</td>
<td>2.48</td>
<td></td>
</tr>
<tr>
<td>bronchioles</td>
<td>0.35</td>
<td>1.07</td>
<td>32</td>
<td>3.11</td>
<td></td>
</tr>
<tr>
<td>bronchioles</td>
<td>0.06</td>
<td>0.17</td>
<td>6 - 10⁴</td>
<td>180.0</td>
<td></td>
</tr>
<tr>
<td>bronchioles</td>
<td>0.05</td>
<td>0.10</td>
<td>5 - 10⁵</td>
<td>10³</td>
<td></td>
</tr>
<tr>
<td>respiratory bronchioles</td>
<td>0.05</td>
<td>0.05</td>
<td>8· 10⁶</td>
<td>10⁴</td>
<td></td>
</tr>
<tr>
<td>conductive zone</td>
<td>0.04</td>
<td>0.05</td>
<td>32</td>
<td>3.11</td>
<td></td>
</tr>
<tr>
<td>transitional and respiratory zones</td>
<td>0.04</td>
<td>0.05</td>
<td>8· 10⁶</td>
<td>10⁴</td>
<td></td>
</tr>
<tr>
<td>alveolar ducts</td>
<td>0.05</td>
<td>0.05</td>
<td>8· 10⁶</td>
<td>10⁴</td>
<td></td>
</tr>
<tr>
<td>alveolar sacs</td>
<td>0.04</td>
<td>0.05</td>
<td>8· 10⁶</td>
<td>10⁴</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.2: A schematic representation of airway branching in the human lung**<sup>5, 10</sup>.

The second region is the conduction zone. This region consists of the first 16 generations of branching. The airways of the conducting zone are described as rigid tubes that consist primarily of cartilage in the walls and that symmetrically divide or bifurcate beginning with the trachea and ending with the terminal bronchioles. The third region is the transitional zone. This region consists of the generations 17 through 19 of the branching. The respiratory bronchioles each consist of a few alveoli in which limited gas exchange occurs. The fourth region is the respiratory zone. This region consists of the generations 20 through 23 of the branching, ending in the alveoli. In the highly vascularised respiratory zone gas exchange occurs by adding oxygen to, and removing carbon dioxide from the blood passing the pulmonary capillary bed.

With increasing generation number, the number of branches rapidly increases, while the distance between the branches and the airway diameter decrease. The summed cross sectional area from mouth to alveolar sacs rapidly increases and results in a trumpet shaped lung model, with a total absorptive surface area of up to 100 m<sup>2</sup>.

### 1.6 Pulmonary ventilation

The inhaled air volume depends on the extent of chest enlargement. During normal breathing,
the inhaled and exhaled volumes (tidal volume) are only a part of the total lung volume. The different parameters describing pulmonary ventilation are shown in figure 1.3. Definitions of the different parameters are given in table 1.1.

![Spirometric tracing demonstrating different measures for lung volumes and capacities. For definitions see table 1.1.](image)

**Table 1.1: Definitions of lung volumes and capacities describing pulmonary ventilation.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (V&lt;sub&gt;T&lt;/sub&gt;)</td>
<td>The volume of air inspired or expired during a normal breath</td>
</tr>
<tr>
<td>Inspiratory reserve volume (IRV)</td>
<td>The maximal volume of air that can be inspired after a normal tidal inspiration</td>
</tr>
<tr>
<td>Expiratory reserve volume (ERV)</td>
<td>The maximal volume of air that can be expired after a normal tidal expiration</td>
</tr>
<tr>
<td>Residual volume (RV)</td>
<td>The volume of air remaining in the lungs after a maximal expiratory effort</td>
</tr>
<tr>
<td>Inspiratory capacity (IC)</td>
<td>The maximal volume of air that can be inspired after a normal tidal expiration (IC = V&lt;sub&gt;T&lt;/sub&gt; + IRV)</td>
</tr>
<tr>
<td>Functional residual capacity (FRC)</td>
<td>The volume of air remaining in the lungs after a normal tidal expiration (FRC = ERV + RV)</td>
</tr>
<tr>
<td>Vital capacity (VC)</td>
<td>The maximal volume of air that can be expired from the lungs after a maximal inspiration (VC = IRV + V&lt;sub&gt;T&lt;/sub&gt; + ERV)</td>
</tr>
<tr>
<td>Total lung capacity (TLC)</td>
<td>The volume of air in the lungs after a maximal inspiratory effort (TLC = IRV + V&lt;sub&gt;T&lt;/sub&gt; + ERV + RV)</td>
</tr>
</tbody>
</table>

Lung volumes are given as the volume of air at body temperature (310 °K), saturated with water vapour at that temperature (BTPS-conditions)

Determination of lung volumes and capacities can provide important information on the pathophysiological status of the lung. The amount of air moving in and out of the lungs
(characterised by V_T, IRV, ERV, VC and IC) can be measured through spirometry. Estimates of volume of air remaining in the lungs after expiration (RV and FRC) are made by gas dilution methods. The respiratory system of a normal adult processes 10-20 m³ of air per day. The gas-exchange area of the lungs is about 120 - 160 m² and is perfused with over 2000 km of capillaries. At rest, about 700 ml of tidal air is inhaled and exhaled with each breath. During heavy work, tidal volume may be three times as much. A resting adult breathes about 12 times per minute and this rate will triple during heavy work.

1.7 Pulmonary mechanics

The ventilatory apparatus consists of the lungs and surrounding chest wall. The chest wall includes not only the rib gages but also the diaphragm and abdominal wall (figure 1.4).

Movement of air into and out of the lungs is driven by pressure differentials or gradients across the lungs. When inspiratory muscles (diaphragm and intercostal muscles) contract to expand the thoracic cavity, a force is applied to the lung surface, which causes expansion of the lungs. Lung expansion occurs because the lungs are compliant and distensible. By expanding, a negative pressure is created within the lungs, specifically in the airways and alveoli. This results in airflow in the direction from high to low pressure, which is in the
direction of the alveoli. Changes in lung pressures relative to atmospheric pressure can be summarised as follows. At the start of inspiration, the alveolar pressure equals atmospheric pressure. There is no pressure difference and thus, no driving force for airflow. In this situation, the relative alveolar pressure is referred to as zero (figure 1.5). Interpleural pressure is about –500 Pa because elastic recoil of the lungs counteracts the forces of the chest wall to recoil outwards. Thus, a negative pressure is generated in the interpleural space between the lungs and the chest wall. Upon inspiration, a greater negative intrapleural pressure is generated as the chest wall moves outward against the elastic recoil of the lungs, reaching a maximal value of about –700 to –800 Pa under normal conditions. The expansion of the lungs by the greater negative intrapleural pressure causes alveolar pressure to decrease (become

\[
\begin{array}{c|c}
\text{volume} & \text{intrapleural pressure} \\
(l) & (Pa) \\
0 & -500 \\
0.5 & -800 \\
\end{array}
\]

**Figure 1.5: Ventilatory parameters during tidal breathing (single breath)**\(^{(5)}\).

negative relative to atmospheric pressure) until it reaches a maximum value of about –100 Pa under normal conditions, providing the pressure gradient for air to flow into the airways and alveoli (depicted as negative flow in figure 1.5). The rate of airflow does not depend on the pressure gradient alone but also on the internal resistance to airflow of the airway system, which is mainly a function of the airway diameters and the existence of obstructions. The obstructions reduce the airway diameters locally, thereby increasing the resistance to airflow. Patients suffering from obstructive diseases have to generate higher pressure differences to
create the same airflow rate, compared to patients without lung obstructions. Consequently, alveolar pressures have to be much lower. During inhalation, the airflow gradually decreases as the alveoli are filled with air and the relative alveolar pressure returns to zero. The difference between intrapleural pressure and alveolar pressure is the transpulmonary pressure, which provides a measure of elastic lung recoil at each point of lung expansion. When inspiration is complete and the lungs are inflated, respiratory muscles relax and elastic recoil properties of the lung cause it to return back to its original state prior to inflation, thereby expelling the inspired air. Intrapleural pressure returns to ~500 Pa and alveolar pressure increases to about +100 Pa, thereby creating the pressure gradient to allow air to flow out of the lungs to the external environment (depicted as positive flow in figure 1.5). Throughout this cycle of normal inspiration and expiration, airways remain open in order to allow air to flow in and out of the lungs with relative ease. Expiration may be forced such as during a cough or when blowing up a balloon, by contracting expiratory muscles (internal intercostal muscles, external and internal oblique abdominal muscles, transversus and rectus abdominis muscles). Such forced expiratory manoeuvres can increase intrapleural pressure to reach positive values, causing a large increase in alveolar pressure above atmospheric pressure and creating a large pressure gradient for air to flow out of the lungs at greater velocity.

1.8 Inspiratory muscle strength

The maximal inspiratory mouth pressure is a measure for the inspiratory muscle strength. In this measurement, maximal inspiratory manoeuvres from residual volume (RV) are performed against a closed shutter. An oval flanged mouthpiece with a small leak is used to prevent the use of the buccinator muscles(12-14). Conventionally, inspiratory muscle strength has been assessed by maximal inspiratory mouth pressure sustained for 1 second (PI\textsubscript{max} or MIP) during a maximal static manoeuvre against a closed shutter(12, 15-20). However, PI\textsubscript{max} is poorly reproducible(21, 22). The peak maximal inspiratory pressure (P·PI\textsubscript{max} or P·MIP) during a maximal static manoeuvre is a more valid assessment of inspiratory muscle strength. This measurement is considered to be influenced less by learning effect and has a high reproducibility(23, 24). Figure 1.6 shows a typical pressure recording during fast maximal inhalation obtained from maximal inspiratory pressure measurement. The peak value is referred to as the peak maximal inspiratory pressure (P·MIP) or P·PI\textsuperscript{max}(23, 24). The plateau value, which has to be maintained for at least one second, is referred to as the maximal inspiratory pressure (MIP) or the PI\textsuperscript{max}.

As shown in figure 1.5 the flow profile in the mouth follows the alveolar pressure profile during ventilation without time delay. The commonly used inhalation-instruction for dry powder inhalers is to inhale forcefully and deeply. Because the airflow through breath-controlled dry powder inhalers depends on the patient-generated inspiratory pressure, the P·MIP might be a useful measure for the peak inspiratory flow through a dry powder inhaler.
In some studies an indication is given that the inspiratory muscle strength might be a determinant for the peak inspiratory flow through breath-controlled DPI's, or a resistance to airflow\textsuperscript{(25-27)}.

Moreover, the respiratory muscles are striated skeletal muscles, which can be trained like other striated muscles in order to increase their strength and endurance. This is demonstrated in healthy volunteers\textsuperscript{(28, 29)} as well as in patients\textsuperscript{(30-33)}. Training with high force contractions increases maximal force, whereas training with high velocity, low force contractions, increases maximal shortening velocity\textsuperscript{(34, 35)}.

![Figure 1.6: Diagram with definitions of peak maximal inspiratory pressure (P·MIP) and maximal inspiratory pressure (MIP).](image)

**1.9 Inhaler devices**

For the generation of aerosol particles in the required size range for deep lung deposition, three different types of inhalation devices are available. These are the nebulizers, pressurised metered dose inhalers (p-MDI) and dry powder inhalers (DPI). p-MDI’s are world wide the most frequently used system and they have proven their value in therapy. In The Netherlands, DPI’s are the most frequently prescribed inhalation device.

**1.9.1 Nebulizers**

Nebulizers are the oldest systems and have been used in inhalation therapy since the early 20\textsuperscript{th} century\textsuperscript{(2)}. Nebulizers are applied for drug solutions or suspensions, which are aerosolised either by air jet or ultrasonic nebulisation. To generate the aerosol from an air-jet nebulizer, compressed air is forced through an orifice over, or in co-axial flow around the open end of a capillary tube. The drug solution or suspension is drawn through the capillary by means of
momentum transfer. In the nozzle region, shear forces disrupt the liquid into small particles that are entrained by the air towards a baffle. Only the smallest droplets, in the desired size range, are able to follow the streamlines of the air and pass the baffle, whereas larger droplets impact on the baffle and are returned to the liquid reservoir. Ultrasonic nebulizers generate aerosols using high-frequency ultrasonic waves by a ceramic piezoelectric crystal. The greatest disadvantages of nebulizers are their poor deposition efficiency, the long inhalation time and the requirement for a power supply. Nebulizers are suitable devices for acute care of non-ambulatory patients and of infants and children(36).

1.9.2 Pressurised-metered dose inhalers

The pressurised-metered dose inhaler (p-MDI) consists of four basic functional elements, container, metering valve, actuator and mouthpiece.

The principle of p-MDI's is based on a spray-can as used for hair spray(3). A liquefied propellant serves both as an energy source to expel the formulation from the valve in the form of rapidly evaporating droplets, and as a dispersion medium for the drug and other excipients(5). Initial droplet size and droplet speed is too high for effective deposition in the lower respiratory tract. Evaporation and deceleration in the upper respiratory tract are essential. For p-MDI's the inhalation manoeuvre is relevant for deposition efficacy. Especially the hand-lung coordination is of major importance. The use of spacer devices or breath-triggered devices overcomes this coordination problem.

1.9.3 Dry powder inhalers

In a United States patent from 1939, by W.B. Stuart, a description is given of what is called the first dry powder inhaler. The patent describes a device, which had been designed to aid the inhalation of aluminium dust for the chelation of inhaled silica. However, the device was never commercialised(37). A patent from 1949, by M.R. Fields, described the first dry powder inhaler to be used for the administration of a pharmaceutical agent. The so-called Aerohaler, was the first commercially available dry powder inhaler for the delivery of isoprenaline sulphate(37).

The first single dose dry powder inhaler with a hard gelatin capsule technology was initially developed for the inhalation of relatively large amounts of drug, being 50 mg of disodium cromoglycate (Spinhaler, 1971)(38). Later, DPI's found their application in inhalation therapy as a CFC-free alternative for the older p-MDI's. However, nowadays DPI's seem to have a much larger potential(4, 39), because of the high lung deposition that can be attained and their suitability for pulmonary delivery of therapeutic peptides and proteins, which can subsequently become systemically available.(40).
Dry powder inhalers basically contain four functional elements, the powder container, the dosing/metering system, the disintegration principle and a mouthpiece. Based on these functional elements, dry powder inhalers can be divided into two major groups, single dose and multi-dose inhalers (table 1.2). The multi-dose inhalers are divided in two different types of design: the reservoir systems and the multiple unit-dose inhalers. An example for the reservoir system is Turbuhaler. In this type of inhaler, the powder formulation is stored in a container from which single doses are measured volumetrically with a special dose-metering unit. Accurate dose metering for this type of inhaler requires careful manipulation of the device by the patient. In the multiple unit-dose inhalers, single doses are filled by the manufacturer into suitable dose compartments, such as blisters. Examples are Diskhaler, having the blisters on a disk (Rotadisk), and Diskus with the blisters on a long strip. Before inhalation, a single blister is either perforated or the cover foil is peeled off the blister foil in order to gain access to one single dose. Another example of a multiple unit-dose inhaler is the Eclipse. This inhaler is actually a single dose inhaler, however it can hold 4 single Spincaps at once.

<table>
<thead>
<tr>
<th>Table 1.2: Dry powder inhalers available on the Dutch market.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaler device</strong></td>
</tr>
<tr>
<td>Single dose inhalers</td>
</tr>
<tr>
<td>Spinhaler</td>
</tr>
<tr>
<td>Rotahaler</td>
</tr>
<tr>
<td>Cyclohaler</td>
</tr>
<tr>
<td>Foradil dry powder inhaler</td>
</tr>
<tr>
<td>Inhalator Ingelheim</td>
</tr>
<tr>
<td>Multi-dose inhalers</td>
</tr>
<tr>
<td>Diskhaler</td>
</tr>
<tr>
<td>Diskus</td>
</tr>
<tr>
<td>Eclipse</td>
</tr>
<tr>
<td>Reservoir systems</td>
</tr>
<tr>
<td>Turbuhaler</td>
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</tbody>
</table>

Single dose inhalers have unit-doses in individual (sealed) dose compartments, usually capsules that have to be placed into the inhaler by the patient. Capsule cap and body must be separated before inhalation (Rotacaps for Rotahaler) or the capsule has to be pierced at both ends, as for the Cyclocaps for Cyclohaler, Inhalettes for Inhalator Ingelheim, or the Spincaps for the Spinhaler.

The powders in the inhaler are in general not formulated as single particles, but as adhesive mixtures or spherical pellets, as described in section 1.10. These mixtures or pellets are suitable for processing and metering. However, the particle size of these mixtures or pellets is far too large for lung deposition. Therefore, the pellet or mixture has to be disintegrated to
make an aerosol cloud, which contains a high fraction of non-agglomerated drug particles with the desired particle size (<5 µm). Many different disintegration principles exist. They may vary from a simple screen (Rotahaler, Diskhaler) (figure 1.7), to twisted powder channels (Turbuhaler) (figure 1.8). The applied disintegration concept in the design of a dry powder inhaler largely determines the resistance to airflow of the inhaler device. In those designs, in which the dry powder formulation is only dispersed into the inspiratory airflow, the inspiratory flow, as energy source, is not used optimally. These type of inhaler designs use a so-called non-specific disintegration system (figure 1.7). Inhalers without a recognisable disintegration principle often have a low resistance to airflow. As a consequence of a non-specific disintegration system the fine particle fraction generated by the inhaler is low. Due to the low resistance to airflow, larger variations in peak inspiratory flow are found. However, the fine particle output is more or less constant over a broad range of inspiratory flows at a low level\(^{41}\).

*Figure 1.7: Schematic diagram of the disintegration of micronised drug particles from carrier crystals through a non-specific disintegration system.*

*Figure 1.8: Schematic diagram of the disintegration of spherical pellets through a specific disintegration mechanism.*
More specific disintegration systems use the inspiratory flow more optimally as energy source for disintegration and delivery of fine particles into the airflow (figure 1.8). This usually results in an increased resistance to airflow of the disintegration system. Due to the inhaler design, the fine particle output depends more strongly on patient inspiratory performance. As a result, the fine particle output is more or less flow dependent. However, the higher resistance to airflow limits the range of possible flow rates, but reduced particle velocity resulted in a reduced mouth and throat deposition. Due to the higher disintegration efficiency, the fine particle output is higher compared to the non-specific disintegration systems.

The mouthpiece may be used to control resistance to airflow of the inhaler and the direction of the aerosol cloud in the mouth and throat, in order to reduce drug deposition in the oropharyngeal cavities\(^{(42)}\).

Dry powder inhalers are generally described as 'breath-actuated' devices, because the inspiratory air steam releases the dose from the dose system and supplies the energy for the generation of fine drug particles from the powder formulation. Because the efficiency of dose release and powder disintegration increases with increasing inspiratory flow rate for most DPI's, it would be better to speak of 'breath-controlled' devices.

In table 1.3 some advantages and disadvantages of dry powder inhalers are summarised.

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\text{Table 1.3: Advantages and disadvantages for dry powder inhalers versus metered dose inhalers\(^{(39)}\).}
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<table>
<thead>
<tr>
<th>Advantages of dry powder inhalers:</th>
<th>Disadvantages of dry powder inhalers:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propellant free</td>
<td>Performance depends on the patients inspiratory flow profile</td>
</tr>
<tr>
<td>Less need for patient coordination</td>
<td>Resistance to airflow of the device</td>
</tr>
<tr>
<td>Less potential for formulation problems</td>
<td>Potential difficulties to obtain dose uniformity</td>
</tr>
<tr>
<td>Less potential problems with drug stability</td>
<td>Less protection from environmental effects and patient abuse</td>
</tr>
<tr>
<td>Less potential for extractables from device components</td>
<td>More expensive</td>
</tr>
<tr>
<td></td>
<td>Not available world wide</td>
</tr>
</tbody>
</table>

1.10 Powder formulations

For the generation of fine particles in the ideal particle size range, the used powder formulation is essential. The flow properties of fine particles in the ideal particle size range is usually poor. In combination with the fact that for the inhaled medication usually very small amounts of drugs have to be accurately metered (6 µg to 500 µg), special powder formulations are necessary to make (free flowing) powders that can be used for processing and metering. For the many marketed dry powder inhalers, only two different types of powder formulations are currently applied. So-called spherical pellets are used in the Turbuhaler. In this type of formulation, the micronised drug particles are agglomerated into much larger
spherical units without binder agent, behaving as a free flowing powder. Some micronised
diluent lactose or glucose may have been added to the active component, but the formulation
does not contain coarser carrier crystals. Spherical pellets can disintegrate nearly completely
during inhalation into much smaller agglomerates or even primary particles that have the
required size-range for deep penetration into the respiratory tract.
The Rotadisk for the Diskhaler, the blisters in the Diskus and the Cyclocaps for the
Cyclohaler are filled with adhesive mixtures. This type of formulation consists of relatively
large carrier crystals, mostly $\alpha$-lactose monohydrate, carrying the micronised drug particles
distributed over their surface. During inhalation, the drug particles have to be released from
the carrier crystals to generate the aerosol with particles of the desired particle size, that are
able to enter the lower respiratory tract. The fraction of drug not detached may cause serious
local side effects, as candidiasis, in the upper respiratory tract (mouth and throat) where the
carrier crystals, and other larger particles, are deposited.

Figure 1.9: Scanning electron micrographs (SEM-photo’s) of dry powder inhaler
formulations. Both pictures on the left hand show an adhesive mixture of 25 mg $\alpha$-lactose
monohydrate with 250µg micronised fluticasone from a Flixotide 250 Diskus
(GlaxoWellcome). On the right hand, the pictures show a spherical pellet of micronised
budesonide from a Pulmicort 200 Turbuhaler (AstraZeneca).
1.11 Deposition mechanisms

After inhalation, particles can be deposited at a great variety of anatomical locations. It is generally accepted that all particles that touch the surface of the respiratory tract are deposited on the site of initial contact. Different physical mechanisms operate on inhaled particles and move them across streamlines of air to the surface of the respiratory tract. These mechanisms are gravitational sedimentation, inertial impaction, Brownian diffusion, interception and electrostatic forces. The deposition in the respiratory tract occurs in a system of changing geometry and at flow rates that change with time and direction\(^\text{(11)}\). The mechanisms that contribute to the deposition of a specific particle depend on the particle’s aerodynamic behaviour, the breathing pattern, geometry of the respiratory tract, and the flow and mixing patterns of the aerosol containing particles and the remaining air in the respiratory tract.

![Diagram of particle deposition mechanisms at an airway branching site.](image)

*Figure 1.10: Particle deposition mechanisms at an airway branching site.*

The three major deposition mechanisms are shown in figure 1.10. During inhalation, the inhaled air changes constantly in direction as it flows from the mouth down through the branching airway system. Particles will have to follow the airstream in order to get deeper into the lungs. However, particles are unable to do so when their inertia is too high, due to a high mass or a high velocity or both, will deposit. Therefore, the largest particles are deposited by the mechanism of inertial impaction in the throat and at the first bifurcations. As the remaining small particles move on into the lung, the air velocity gradually decreases to much lower values and the force of gravitation becomes important. Settling by sedimentation is the dominant deposition mechanism in the deeper airways. The finest particles are able to enter the periphery of the lung, where they can make contact with the walls of the airways as
the result of Brownian motion (diffusion). Near obstructions or in the small airways, drug deposition might occur due to particle interception, because the particles touch the airway surface, although they do not deviate from their streamlines. A charged particle may deposit in the respiratory tract by electrostatic forces. Though the contribution of these latter two deposition mechanisms is considered to be low.

1.12 Particle size for lung deposition

For a prediction of the lung deposition of inhaled particles, two mechanisms have to be taken into account. Firstly the penetration probability of particles into the lung, and secondly the deposition efficiency. The penetration probability is the probability that a particle of a certain size is able to pass the lung bifurcation’s and penetrate further into the lung. The penetration probability for the defined target area of the terminal and respiratory bronchioles, will increase with decreasing particle diameter (figure 1.11, dark curved area). On the other hand, deposition efficiencies have to be taken into account. Deposition efficiencies for particles in the respiratory tract are generally presented as function of their aerodynamic diameter. In the definition of the aerodynamic diameter, corrections are made for density differences from unity and shape irregularities of the particles. Large particles (>10 µm) are removed from the airstream with nearly 100% efficiency by inertial impaction, mainly in the oropharynx. But as sedimentation becomes more dominant, the deposition efficiency decreases to a minimum of

![Figure 1.11: Penetration probability and deposition efficiency dependence on particle diameter in the respiratory tract. The black line is the deposition efficiency. The dark curved area is the penetration probability in the terminal and respiratory bronchioles. The grey area is the optimal particle size, of which the shaded area is mostly mentioned as preferred particle size.](image)
approximately 20% for particles with an aerodynamic diameter of 0.5 µm (figure 1.11, black line). Only when particles become smaller than 0.1 µm the deposition efficiency increases again as a result of diffusional displacement. It is believed that 100% deposition due to Brownian motion might be possible for particles in the nanometer range\textsuperscript{(43)}. From the penetration probability and the deposition efficiency, as well as from deposition studies and force balances, it can be derived that the optimum (aerodynamic) particle size lies between 0.5 and 7.5 µm (figure 1.11, grey area). Within this approximate range many different sub-ranges have been presented. The sub-range of 1 to 5 µm\textsuperscript{(44)} (figure 1.11, shaded area) is considered to be the preferred particle size range in this thesis. Particles of 7.5 µm and larger mainly deposit in the oropharynx, whereas most particles smaller than 0.5 µm may be exhaled again. All inhalation systems for drug delivery to the respiratory tract produce polydisperse aerosols of which different amounts of the delivered fine particles are in the range of the ideal particle size.

1.13 Inhalation-instruction

The pulmonary delivery of drugs by inhalers is, compared to the oral delivery route, a complex therapy for the patient. Using the oral route of administration, it may be sufficient to give the patient a dosing schedule for taking one or more tablets at predetermined times of the day. Using an inhaler, this is not enough, and the patient also has to receive an adequate inhalation-instruction to ensure correct inhalation of the medication.

Differences in the inhaler-designs cause large differences in the instructions for correct use of these inhalers. The way in which the patient uses the inhaler is also called the patients' inhalation-technique. It has frequently been shown that patients suffer from problems with their inhalation-technique as well as from problems regarding compliance. In a number of studies concerning the inhalation-technique of asthma and COPD patients it is shown that 70 to 80% of the patients were able to perform the most important manoeuvres with their inhaler correctly. A correct execution of all manoeuvres could only be performed by a much smaller fraction of the patients\textsuperscript{(45)}. Mistakes are made, ranging from mistakes in loading the inhaler, to mistakes in performing the inhalation. Exhaling through the inhaler before inhalation, not releasing the dose before inhalation, or mistakes in storage of the inhaler have been reported\textsuperscript{(45-48)}. General practitioners, chest physicians, pharmacists, and lung-function nurses are the appropriate persons to give inhalation-instructions to patients. As a result of good inhalation-instructions to the patient, the number of mistakes in the patients' inhalation-technique reduces significantly, which results in an increased therapeutic efficacy of the inhalation therapy\textsuperscript{(45-50)}.

The use of different types of inhalers by one patient, for the inhalation of bronchodilators and corticosteroids, may cause many mistakes in the inhalation-technique\textsuperscript{(45)}. When using different types of inhalers, the importance of a proper inhalation-instruction increases, since
the patient has to perform the correct inhalation-technique for each inhaler. For convenience of the patient, and to prevent the patient from making mistakes, it is recommended to give one patient only one type of inhaler (if possible) for the bronchodilators and the corticosteroids.

1.14 Patient compliance

The term patient compliance in a medical context is generally defined as the extent to which the patients' medication taking history corresponds to the prescribed drug regimens, thereby following the instructions of the health care provider\(^\text{51-55}\). Variable patient compliance is recognised as a potential complication in patient care\(^\text{9, 52}\). The compliance of patients with a chronic disease, including respiratory diseases, is often inadequate. Compliance with maintenance therapy, such as inhaled corticosteroids, of which the effect is noticeable only after a period of weeks, may be less than compliance with drugs that relieve asthma symptoms more rapidly\(^\text{9}\). Therefore, for inhaled corticosteroids, studies mainly focus on underuse of the medication compared with the prescribed dose. Patient compliance can be calculated from prescription data by dividing the delivered amount of doses by the required amount of doses in a defined period. This calculation of patient compliance result in three classifications of compliance, as given in table 1.4.

<table>
<thead>
<tr>
<th>compliance</th>
<th>definition</th>
</tr>
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<tbody>
<tr>
<td>appropriate use</td>
<td>the patient takes the medication in a way that conforms satisfactorily to prescribed use</td>
</tr>
<tr>
<td>(compliant)</td>
<td></td>
</tr>
<tr>
<td>underuse</td>
<td>the patient takes less medication than prescribed</td>
</tr>
<tr>
<td>overuse</td>
<td>the patient takes more medication than prescribed</td>
</tr>
</tbody>
</table>

Patient compliance depends on different parameters, especially parameters directly related to patients’ behaviour. Health care providers might influence this behaviour by appropriate prescribing, patient education and counselling. The prescribing behaviour of the general practitioner is directly related to the choice of the inhaler device and the prescribed number of doses to be taken every day. An appropriate inhalation technique will significantly affect compliance of the patient, but compliance may also depend on the age of the patient and patients’ awareness and beliefs\(^\text{56}\) on the need of a proper inhalation technique. The pharmacist may influence the patient compliance by patient education and counselling. To optimise inhalation-instruction and patient compliance, networks including general practitioners, pharmacists and chest physicians should make agreements on these subjects. An optimal patient education and counselling may finally improve the inhalation technique and the patient compliance, and thereby therapeutic efficacy of the inhalation therapy.
1.15 Prescribing

Besides the choice of drug in the treatment of asthma and COPD, the choice of the inhaler device plays an important role in the success of the therapy. From several studies, it is known that therapeutic decision making is usually based on habits\(^{(57-64)}\). Many drug choice models show that habitual prescribing is the most common way of prescribing. In this habitual prescribing, each physician uses only a limited number of devices in their prescription, the so-called evoked set.

The drug choice process for the treatment of a particular disease is divided in two steps (figure 1.12). Firstly, a small set of possible treatment options for the proposed problem is generated, the so-called evoked set. Secondly, a therapy is selected for a specific patient\(^{(57)}\).

\[\text{Problem} \rightarrow \text{Evoked Set} \rightarrow \text{Therapy choice}\]

*Figure 1.12: The drug choice process\(^{(57)}\).*

As a result of evoked set based on prescribing, only a limited number of drugs are routinely prescribed by the individual prescriber. Once it has been decided to prescribe a drug, a few names automatically pop-up\(^{(57, 65)}\). The evoked set provides a number of possible treatments, from which finally one therapy is selected for a specific patient. The physicians may choose a drug through habitual or non-habitual choice (figure 1.13). Most of the choices for a brand are probably done by habitual choice\(^{(62)}\). When the therapeutic situation is new for the physician, he will probably choose a drug non-habitually by active problem-solving (figure 1.13). This can also be expected to occur when the therapeutic outcome of a previous prescription is unsatisfactory, either because of insufficient efficacy, or because of side effects. After a number of satisfactory results, the physician will choose the drug habitually when confronted with the same situation.

\[\text{Evoked Set} \rightarrow \text{Choice of therapy}\]

*Figure 1.13: Choosing from the evoked set\(^{(57)}\).*

The concept of the evoked set is also applicable to the choice of an inhaler device. Many of the prescriptions for the treatment of asthma or COPD are given habitual. However, the difficult interaction between patient and inhaler device combined in the inhalation
characteristics suggests that, for the treatment of asthma or COPD, active problem-solving is a more appropriate choice. Besides knowledge about the applied drug in the treatment, also technical knowledge about the applied inhaler device is necessary for an optimal choice of an inhaler device.

1.16 References

8. ATS Statement. Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 1995;152(5):s77-s120.


