CHAPTER 1

GENERAL INTRODUCTION
Chapter 1

1.1. Introduction

The respiratory tract is one of the oldest routes for the administration of drugs. Therapeutic aerosols, smoke and vapours of volatile substances (e.g., from steam baths) have been inhaled for many centuries. Pulmonary administration is attractive for a variety of reasons, not only for local therapy in the lungs, but also for systemically acting drugs.

Major advantages when considering local therapy are:

1. The drug is delivered directly to the target area, which enables a rapid and predictable onset of action.
2. The delivery to the target area enables reduction of the dose (compared to oral or parenteral administration) which also reduces systemic side effects.

And considering systemic action:

3. Administration through the respiratory tract is non-invasive.
4. First-pass metabolism by the liver and degradation within the gastrointestinal tract can be avoided.
5. The large surface area of the alveoli (40-100 m$^2$) and the thin barrier for absorption promote the rapid uptake in the bloodstream for molecules with a molecular weight up to approximately 20 kDa (Patton, 1996).

The history of inhalation therapy can be traced back to 4000 years ago, when in India the leaves of the *Atropa Belladonna* plant were smoked as a cough suppressant (Grossman, 1994). Stramonium cigarettes (prepared from the dried leaves and flowering tops of the plant *Datura Stramonium*) in various brands were smoked until the 1950s (e.g., Fig. 1A). The antecedents of contemporary inhalation therapy stem from the nineteenth century with the invention of the glass bulb nebulizer and portable jet nebulizers which evolved as a great variety of devices (e.g., Fig. 1B) (Grossman, 1994). Since the second half of the 20th century, nebulizer technology has developed rapidly due to the widespread introduction of electric compressors. Jet nebulizers were followed by ultrasonic nebulizers in the 1960s and the first medical metered dose inhaler (MDI) was developed around the same time (1956, Medihaler®, Riker). However, the use of ozone layer depleting chlorofluorocarbon (CFC-) propellants appeared to be a major drawback of the first generation MDI’s (Fink, 2000). In the Montreal Protocol (1987), it was agreed to substitute hydrofluoroalkane (HFA-) for propellants which rendered the reformulation of MDI-formulations necessary.

Almost twenty years after the presentation of the medical MDI, the first dry powder inhaler (DPI: Fisons Spinhaler®) was introduced onto the market (1970) (Ashurst et al., 2000). Since its introduction, many different types of devices have been developed which are frequently categorized into unit-dose and multi-dose DPI’s. Different technologies from various disciplines have been used in these developments, which were stimulated by the dramatic increase in the
number of patients diagnosed with asthma and chronic obstructive pulmonary disease (COPD) in the twentieth century. Other very important stimuli for DPI-development in the late 1980’s were the previously mentioned banning of CFC-propellants in MDI-formulations and the desire to find a non-invasive route for the administration of drugs that can’t be administered orally or have a low bioavailability via the oral route, like therapeutic proteins and peptides for systemic action (Byron and Patton, 1994; Patton et al., 1999; Zijlstra et al., 2004; van Drooge et al., 2005). In the past decade, attention has particularly focussed on the pulmonary route for such drugs, which offers several advantages over the oral or parenteral route (Adjei and Gupta, 1994; Davis, 1999). More recently, physicists in Canada recommended that nebulizers should not be used for SARS-patients since their use could cause transmission of the disease, which opens the path for dry powder inhalers also in the treatment of SARS-patients (Dwosh et al., 2003).

The requirements for effective penetration and deposition of aerosol particles in the respiratory tract are well known. They can be derived from the many modelling studies on particle behaviour in the respiratory tract (Brain and Valberg, 1979; Hinds, 1982; Schlesinger, 1985; Martonen and Katz, 1993; Katz et al., 1999; Kim, 2000; Suarez and Hickey, 2000). In addition, many deposition, efficacy or pharmacokinetic studies are available from which the preferable aerodynamic size distribution of the drug particles (or droplets) and inhalation manoeuvre can be estimated (e.g. Zanen et al., 1994, 1995; Brand et al., 2002).

Mostly, particles in the aerodynamic size range between 1 and 5 micrometer (µm) are recommended (Clarke and Newman, 1983; Byron, 1986; Zanen et al., 1992; Timsina et al., 1994), whereas slow inhalation and a prolonged period of breath hold after inhalation are known to improve fine particle penetration and deposition in the small airways (Brand et al., 2000).
The requirements for the aerodynamic size distribution of the aerosol and the inhalation manoeuvre are determined by the aerodynamic behaviour and deposition mechanisms of the particles in the aerosol. The deposition mechanisms can be explained with simple fluid and particle dynamics in the respiratory tract, which consists of a branching system of airways from the trachea to the alveoli (e.g. Hinds, 1982). As a result of the many branchings (23 to 26 in total), the cross section for air flow increases exponentially from the trachea to the alveolar sacs. Accordingly, the air velocity decreases from nearly 4 m/s in the trachea to less than 1 mm/s in the alveoli (at a moderate inspiratory flow rate of 60 l/min). This has the consequence that the air flow is turbulent in the upper tract and laminar further downstream. In the upper tract, where the air velocity is still relatively high, particles may collide with the inner walls of the large airways by inertial deposition. Particles with high inertia (large diameter; high density) are unable to follow the airflow in bifurcations and bends and deposit on the mucosa covering the inner airway walls. Filtering of the larger particles in the upper tract in combination with the reduced velocity decreases the deposition probability by inertial impaction further downstream, and increases the contribution of sedimentation to total deposition. However, the gravitational settling velocity of particles in the micron range is low, whereas their residence time in the lungs is relatively short. As a result, the deposition efficiency decreases as particle settling becomes more dependent of sedimentation than of inertial impaction. Deposition efficiency under normal breathing conditions reaches a minimum of only approximately 20% for particles of 0.5 µm, meaning that 80% of particles of this size are exhaled again. To increase the deposition efficiency, the residence time can be prolonged, which explains the benefit of a breath hold period in this respect. For particles smaller than 0.1 µm, the efficiency may increase also due to an increasing contribution of Brownian motion to particle deposition. However, there is no experimental evidence for this phenomenon jet.

Because filtering of airborne particles in the upper tract by inertial deposition depends on the particle’s aerodynamic diameter and the particle velocity, the cut-off value of the upper tract depends on the inhalation manoeuvre. At higher flow rates (> 60 l/min), most particles larger than 3 to 5 µm can not pass the oropharynx and the first bifurcations, but when the flow rate is decreased (to less than 30 l/min), particles in the size range up to 3-5 µm may enter the central or even the deep lung (Brand et al., 2002). If such particles are able to enter the lung periphery, their deposition efficiency will be relatively high due to their high sedimentation velocity (compared to particles of 1 µm or smaller). The decreasing sedimentation velocity with decreasing particle size is the reason why particles smaller than 1 µm are often considered unsuitable for inhalation, which explains why the recommended aerodynamic size range is between 1 and 5 µm.

The relationship between aerodynamic particle size and deposition has been studied extensively (Rees et al., 1982; Heyder et al., 1986). Most studies
confirm the computations in their predictions that the most effective particles for inhalation are indeed within the aerodynamic size range of 1-5 µm (Byron, 1986; Ganderton, 1992; Timsina et al., 1994; French et al., 1996; Suarex and Hickey, 2000). In this respect, it must be realized that particles with larger geometric diameters may be useful for inhalation if they have low densities, e.g. as the result of porous structures (Edwards et al., 1997; Ben-Jebria et al., 1999). Such particles may have an aerodynamic diameter between 1 and 5 µm, although their geometric diameter is much larger (e.g. in the size range of 10 to 30 µm) (Vanbever et al., 1999; Dunbar et al., 2002).

The three types of inhalation devices (nebulizers, MDI’s and DPI’s) mentioned above in the historical review, produce different types of drug aerosols at different conditions. Nebulizers and MDI’s are not the subject of this thesis and therefore, they will not be described and explained in detail. The aerosols produced by these devices consist of small droplets containing the drug either in solution or in suspension. In general, the droplet size distributions of aerosols generated by jet nebulizers are relatively wide (up to 80 µm). For this reason, baffles are used which collect (and recirculate) the largest droplets. However, these baffles also reduce the output rate. The rather unfavourable size distribution and substantial losses of aerosol to the environment during periods of exhalation, limit the lung deposition to (on average) less than 10% (Selroos et al., 1996; Le Brun et al., 2000). The droplets from CFC-MDI’s are discharged with a high inertia (high velocity in combination with a large initial diameter). This leads to high oropharyngeal depositions, unless extension tubes or spacer devices are used (Newman et al., 1984; Vidgren et al., 1987a; Bisgaard et al., 2002). For patients who find it difficult to coordinate between inhalation and MDI actuation (dose release), a dose may be fired into a spacer device first. The spacer acts as a reservoir for the aerosol which can be inhaled slowly (Toogood, 1994). However, spacer devices may also contribute to losses, due to impaction, sedimentation and electrostatic attraction (Bisgaard et al., 2002). Breath actuated MDI’s offer another alternative to solve coordination problems (Price et al., 2003).

The inspiratory air is the transport medium for the aerosol into the lungs, but it also delivers the energy for aerosol generation in most DPI’s, as will be explained in subsequent paragraphs. Because the kinetic energy increases with increasing flow rate, the fraction of the dose from a DPI that has the desired particle size distribution (fine particle fraction: FPF) may depend on the flow rate. A substantial increase in FPF may also occur when the available energy is utilized more effectively. This confronts the DPI-scientist with what seem to be paradoxical requirements. On the one hand a high flow rate is desired for a high FPF; on the other hand the part of FPF that enters the target area decreases with increasing flow rate. This paradox has led to many misconceptions. For example, DPI’s with a more or less flow rate independent FPF have been developed for constant therapy. Recently, it has been shown that an increasing FPF with increasing flow rate may
compensate for a shift in drug particle deposition to higher airways, meaning that in fact an increasing FPF yields a more constant therapy (de Boer et al., 2005b; Frijlink and de Boer, 2005).

This thesis presents the work performed on powder formulations for DPI’s, which contain the drug particles in the desired aerodynamic size distribution. To make this work comprehensible, an introduction is given into the design and working principle of dry powder inhalers in this first chapter. Different types of powder formulations are discussed, of which adhesive mixtures have been the subject of the experimental investigations presented and discussed in the chapters 2 to 6. A summary of the history of adhesive mixtures is given, as well as a literature review regarding the factors that influence the performance of this type of formulation in dry powder inhalers. This review describes the state of the art before the investigations (chapters 2-6) were started.

1.2. **Dry powder inhalers: design and working principle**

Dry powder inhalers consist at least of four main parts, which are basically the same for all types of currently marketed inhalers (Frijlink and de Boer, 2004). These main parts are the powder formulation, a dose measuring system, a powder de-agglomeration principle which releases fine drug particles from the powder formulation during inhalation and a mouthpiece (as shown in Fig. 2). Each of these parts affects the inhaler efficiency with respect to dose dispensing and powder de-agglomeration, and thus the amount of drug particles that can theoretically reach the deeper parts of the lung for deposition (Byron, 1986; Timsina et al., 1994).

![Fig. 2: Primary functional design elements of a dry powder inhaler (de Boer et al., 2005a)](image-url)
As explained in § 1.1., drug particles need to have an aerodynamic particle size within the range between 1 and 5 µm. Micronized drug particles are very adhesive and cohesive however, and as a result, they have extremely poor flow properties. They tend to stick together and to other surfaces they make contact with. Inhalation drugs are furthermore given in low doses, varying from a few micrograms, to a few milligrams. This combination of low dose, stickiness and poor flow properties makes it impossible to obtain good dose reproducibility without further processing of the drug particles into a suitable powder formulation. Processing has the objectives to improve the flow properties and to reduce the co- and adhesiveness and basically refers to size enlargement by agglomeration with or without the addition of excipients. Two types of formulations are frequently used in dry powder inhalation, as shown in Fig. 3A-C. They are named soft spherical pellets and adhesive mixtures.
In soft spherical pellets (Fig. 3A), the micronized drug particles are agglomerated (with or without micronized lactose (or glucose) particles) into much larger units (without binding agents). After controlled size enlargement, the agglomerates are spheronized and sieved into an approximate size range of 200-2000 µm. Spherical pellets are easily disintegrated on impact due to their high porosity (60-80%) and poor mechanical stability (Boerefijn et al., 1998). In an inhaler, this can be a disadvantage, because the pellets may also disintegrate when the inhaler is accidentally dropped which influences the dose measuring accuracy and efficiency.

In adhesive mixtures (the type of formulation investigated in this thesis) micronized drug particles are distributed homogeneously over the surface of large carrier particles, usually alpha lactose monohydrate crystals (Fig. 3B) (Ganderton and Kassem, 1992). However, other types of lactose have been proposed as drug carrier, e.g. spray-dried (Kawashima et al., 1998a; Heng et al., 2000), roller dried (β anhydrous) (Vanderbist et al., 1997) or agglomerated lactose (Fig. 3C) (Ellison et al., 2000; Dickhoff et al., 2002). Also other carrier materials, like mannitol, glucose, trehalose, sorbitol, maltitol and xylitol have been explored as carrier for inhalation powders (Braun et al., 1996; Chew and Chan, 1999; Tee et al., 2000; Bosquillon et al., 2001; Steckel and Bolzen, 2004). Lactose is the only carrier material used in marketed formulations so far, mainly because of its non-toxicological behaviour (Baldrick and Bamford, 1997) and the acceptance by registration authorities for this purpose. Carrier size fractions are selected on their flow properties in order to obtain good dose measuring reproducibility, but also on their interaction properties with the drug particles, because sufficient fine drug particles have to be attached during the formulation process and subsequently detached from the carrier crystals during inhalation. This process of drug particle detachment is described as de-agglomeration. The extent of drug particle detachment depends on many different parameters which are explained and discussed in the chapters 2-6.

The powder formulation can be stored in a bulk container, in small blisters or capsules into which single doses are weighed. Bulk containers carry relatively large amounts of powder from which the patient has to isolate single doses by operating a dose measuring system. This can be measuring of a fixed volume of powder in a slide (as for the inhaler shown in Fig. 2) or any other type of lock system. Filling of the lock from the powder reservoir is often by the force of gravity and therefore, reproducible dose measuring requires not only good flow properties of the powder, but also that the inhaler is kept in the correct position during dose measurement. Because of the large number of doses carried in the container, DPI’s with such containers are referred to as multi-dose inhalers. Blisters are often arranged in small numbers (4 to 60) on disks or strips which makes them multiple unit-dose inhalers and capsule inhalers are mostly single-dose DPI’s. The dose (measuring) system must be designed and used in such a way that
the entire drug dose can be entrained by the air stream passing through the inhaler during inhalation. To make this possible, blisters and capsules have to be perforated (or opened). Subsequently the dose has to pass the de-agglomeration principle of the inhaler.

The energy source for de-agglomeration in most dry powder inhalers is the inhaled air stream. The kinetic energy is used to generate shear, lift, friction and inertial forces (Amass, 1996; Voss and Finlay, 2002). Of these forces, inertial forces are the most effective for adhesive mixture type of formulations (de Boer et al., 2003a). They are proportional to the third power of the drug particle diameter and they are also effective when carrier particles with a high surface rugosity are employed. This, in contrast with shear, drag, lift and friction forces which can only get hold of drug particles that project from the carrier surface. Particles in carrier surface discontinuities may find shelter from these forces. Drag and lift forces are generated in turbulent flow areas, or by air flows directed perpendicular to the carrier surface, as for instance in the GlaxoSmithKline Diskus® Inhaler. They are the result of a velocity difference between the carrier particle and the air flow over the carrier surface and generation of these forces requires (for instance) impacting air streams, local flow constrictions or tortuous channels, which all influence the air flow resistance of the inhaler. Tortuous or helical channels may also be used to generate shear and friction forces, which are particularly effective for the de-agglomeration of spherical pellets (e.g. AstraZeneca Turbuhaler®). Particles sliding along the inner walls of the helical channel disintegrate mainly by internal shear (due to the combined action of the drag and friction force). Inertial forces may be the result of particle-particle collisions or collision of particles with flow baffles or inhaler walls. When carrier crystals collide, adhering drug particles are decelerated and the detachment forces acting on the drug particles depend on the initial carrier velocity and the drug particle mass. Special concepts for generating inertial forces are cyclone or classifier chambers. In such circulation chambers not only collision forces may be generated, but also centrifugal and friction forces may play a role. In addition, the time during which, and the direction in which the detachment forces act may be sustained and varied respectively (de Boer et al., 2003a; de Boer et al., 2005a). The de-agglomeration efficiency of the inhalers may increase (higher fine particle output) with increasing flow rate through the inhaler when shear, friction and inertial forces are applied (Zanen et al., 1992; Hindle et al., 1995; Srichana et al., 1998). When drag and lift forces are used, the flow rate is less important.

The mouthpiece can be designed to control the resistance to the airflow of the inhaler, e.g. by adding a bypass flow to the aerosol cloud from the inhaler. If the bypass flow is arranged as a sheath of clean air around the aerosol cloud, it may even reduce the fine particle deposition in the mouth from back flows (de Boer et al., 1997). This is particularly favourable when the aerosol has a tangential flow component, as for classifier, cyclone or helical insert inhalers, which causes the aerosol flow from the inhaler to diverge upon discharge from the mouthpiece. On
the other hand, such a tangential flow component has the advantage that particles with high inertia, such as carrier particles in adhesive mixtures, are deposited in the mouth instead of in the throat, from where they can easily be rinsed with water. This prevents the occurrence of local side effects in the throat, like hoarseness and candidiasis which are the most frequently reported side effects related to corticosteroid inhalation therapy.

1.3. Adhesive mixtures

The predominant forces between drug and carrier particles in adhesive mixtures are van der Waals' forces (Visser, 1989; Hickey et al., 1994). These van der Waals' forces act over short distances (0.2 – 1.0 nm) between solid surfaces. However, other forces can also occur to yield attraction or interaction between solid particles, such as coulombic (electrostatic) forces, capillary forces due to liquid bridges, mechanical forces (resulting from interlocking or irregularly shaped particles) and solid bridges (when individual particles have been joined at points of contact by sintering, re-crystallization or chemical reaction). The type and order of magnitude for the interaction forces between drug and carrier may be influenced by discontinuities and impurities of the carrier surface and by the action of friction and impact forces during the mixing process (preparation of the adhesive mixture).

1.3.1. Adhesive mixtures reported in the literature

The history of adhesive mixtures goes back to the period between 1965 and 1985. Initially, these mixtures were described as ordered mixtures. Jones and Pilpel, (1965) were among the first to show that particles smaller than 50 µm tend to adsorb onto surfaces of larger host or carrier particles in a powder mixture between the both. Travers and White, (1971) observed that this process prevents segregation and that adhesive mixtures may exhibit a higher degree of homogeneity than would be expected on the basis of homogeneity equations derived for random mixtures (Lacey, 1943; Buslik, 1973). For this reason, adhesive mixtures were considered favourable for tabletting (Hersey, 1975; Yeung and Hersey, 1979; Staniforth, 1987). Hersey (1975) introduced the term ‘ordered mixing’ when he recognized that the adhesion of fine particles onto the surface of larger carrier particles is basically a different mixing concept than random mixing between non-interacting particles.

In 1980, Stephenson and Thiel explained that the formation of an interactive mixture (adhesive mixture) is a two-step process. The fine (cohesive) particle agglomerates must first be broken down into single particles during the mixing process before these can adhere to carrier crystals. Staniforth, (1981) in his ‘total mixing concept’, described that mixing of fine and coarse particles together leads to a dynamic equilibrium between an adhesive and non-adhesive mixture. Aulton and Clarke's, (1996) description of a competition between cohesion and adhesion is in agreement with Staniforth’s ‘total mixing concept’. Staniforth,
(1987) extended this thinking with his ‘order out of chaos’ theory. This theory includes the notion that the outcome of the competition between cohesion and adhesion is uncertain. He explained that the equilibrium may change in the direction of adhesion by size reduction of both components or by enlargement of the surface of the coarse component. The latter can be achieved (for instance) by increasing the rugosity of the carrier particle surface. Onto such surfaces, adhesion through multiple contacts can occur. This reduces removal of the adhering fines due to abrasion. Staniforth based his theory on the finding that large particles of recrystallized lactose with a more porous structure than much smaller crystalline carrier particles exert stronger adhesion forces between the drug and carrier particles and therefore, result in more stable mixtures (Staniforth et al., 1982). Others found identical results with mixtures containing carriers with high rugosities (Wong and Pilpel, 1990; Johnson and Zhang, 1997; Swaminathan and Kildsig, 2000). It has been confirmed by scanning electron microscopic investigation that drug particles indeed seem to assemble in the carrier surface discontinuities during mixing of the carriers with a high rugosity (Kulvanich and Stewart, 1987).

1.3.2. Adhesive mixtures for dry powder inhalation

The objectives of early adhesive mixture studies were different from that of most current studies on inhalation powder mixture in that they were primarily focused on maximal mixture stability and homogeneity. Although these aspects are also relevant to inhalation powders, a third aspect may even be of greater importance. The research on adhesive mixtures for inhalation has to be focused on achieving an optimum between the homogeneity, stability and particularly drug particle detachment during inhalation. This requires balancing between the adhesive forces in the mixture and the detachment forces generated during inhalation, as has recently been explained with the introduction of a novel Force Distribution Concept (de Boer et al., 2003a; Frijlink and de Boer, 2004). Drug and carrier properties, carrier payload, mixing conditions and inhaler design may all be relevant to this balance, as will be reviewed in the following paragraphs.

1.3.2.1. The relevance of carrier surface rugosity, shape and impurities

Most attempts to increase the fraction of drug particles released from carrier crystals during inhalation have been made by influencing the physico-chemical properties of the carrier particles (Podczeck, 1998a; Karhu et al., 2000; Harjunen et al., 2002). Surprisingly, most researchers focused solely on controlling the shape and/or surface (roughness, impurities and polymorphism) of the carrier particles. This was primarily based on the expectation that carrier pores, clefts and cavities (carrier surface discontinuities in general, expressed as carrier rugosity) and impurities (e.g. ductile surface layers of peptide and protein residues from the mother liquor, containing relatively high amounts of adsorptive water) are the dominant factors in the interaction between drug and carrier particles. Such sites of
high rugosity and impurity may exhibit multiple contact points and increased contact areas with the drug particles as well as capillary forces. They are often described as ‘active sites’, being sites with an increased binding force between the drug and carrier particles. For this reason, it has been recommended to use smooth and clean carrier particles, since increasing the smoothness may increase the drug particle detachment during inhalation (Kassem and Ganderton, 1990; Kawashima et al., 1998a; Podczeck, 1998a; Zeng et al., 2000a; Zeng et al., 2001b). However, it has also been postulated that there may be an optimum in the (type of) carrier smoothness or rugosity (Ganderton and Kassem, 1991; Vanderbist et al., 1997; Heng et al., 2000; Young et al., 2002). This may explain why smooth carrier surfaces (or carriers with small cavities in the submicron range) can produce both lower (Zeng et al., 2001b) and higher drug depositions (Kawashima et al., 1998a).

Smooth carrier particles can be made with special preparation techniques. These techniques include crystallization from carbopol gels (Zeng et al., 2001a), temperature controlled etching (El-Sabawi et al., 2004) or surface treatment of the carrier crystals by submersion in ethanol solutions (Zeng et al., 2001b; Iida et al., 2003). Recently, it has been shown that it depends also on the type of detachment forces during inhalation whether a high carrier rugosity decreases drug particle detachment during inhalation or not. Inertial detachment forces may be effective in removing drug particles even from large carrier cavities (de Boer et al., 2003b). This is particularly an advantage when the drug particles are present (in these cavities) as small agglomerates, which have a much higher inertia than primary particles. Therefore, they are subjected to much higher detachment forces (Louey et al., 2003). Because in most of the previously mentioned studies inhalers were used with de-agglomeration principles based on drag, lift and shear forces to detach the drug particles from the carrier, it can be understood that the carrier surface properties are considered to be the most important factor in the drug-to-carrier interaction. The effectiveness of these inhalers in detaching drug particles from the carrier surface is strongly reduced when surface irregularities exist, inside which the drug particles find shelter from these types of forces acting along the carrier surface.

Also the shape of the carrier particles has been found to influence the drug particle detachment in inhalers based upon turbulent shear for drug particle detachment (Zeng et al., 2000a; Larhrib et al., 2003b). However, it should be mentioned that these carrier particles were prepared using special crystallization techniques yielding smoother surfaces than marketed carrier products and hence, more than one parameter was varied.

Mixing with isoleucine or magnesium stearate may be another way to influence the drug-carrier interaction (Colombo et al., 2000; Young et al., 2002), as these substances occupy the active carrier sites. This aspect will be discussed more in detail in § 1.3.2.5.
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1.3.2.2. The relevance of carrier particle size and size distribution

Next to the carrier surface properties, other parameters have been investigated that influence the interaction between drug and carrier particles in adhesive mixtures. Carrier particle size distribution appears to be particularly relevant in this respect (Kulvanich and Stewart, 1987; Chew and Chan, 1999; Podczeck, 1999; Karhu et al., 2000). It is possible to obtain lactose carrier fractions in a wide range of diameters, but in a number of studies, a typical carrier lactose size fraction of 63-90 µm has been used (e.g. Larhrib et al., 1999). It has been shown that the in vitro respirable fractions obtained from finer carrier fractions are generally higher than those from coarse carrier fractions (Ganderton and Kassem, 1992; French et al., 1996; Steckel and Müller, 1997; Islam et al., 2004). Many different explanations can be given for this finding. For instance, it has been reported, that the size of the carrier surface discontinuities as well as the amount of carrier impurities per unit surface area of the carrier crystals increase both with the mean diameter of the crystals (de Boer et al., 2002c; de Boer et al., 2003b). As explained in the previous paragraph, a high carrier rugosity (and impurity) may increase the magnitude of the adhesive forces and also reduce the effectiveness of detachment forces during inhalation. It is also known that press-on forces, the forces with which drug particles are pressed onto the carrier crystal during mixing, may increase the adhesive force between the drug and carrier particles (Lam and Newton, 1992; Podczeck, 1996). Coarser carrier particles, and also narrow size fractions of relatively small particles, exhibit much higher friction and collision forces during the mixing process than fine carrier particles, or carrier fractions with a wider size distribution. These forces may act as press-on forces, although this depends on the carrier payload and carrier rugosity too.

The finding that fine carrier fractions are preferable compared to large carrier fractions is particularly valid for inhalers generating turbulent shear forces. In inhalers based upon inertial forces, also coarse carrier fractions may yield high fine particle fractions. One of the reasons is the previously mentioned high efficacy with which inertial detachment forces can remove drug particles from carrier surface discontinuities. If the inertial detachment forces are generated in a classifier type of inhaler, decreasing the carrier particle diameter may also reduce the particle velocity in the classifier due to tribocharge. Such inhalers produce higher fine particle fractions when the action of the detachment forces is prolonged, e.g. by establishing a certain residence time for the powder in a classifier (de Boer et al., 2003a). The residence time generally increases with increasing mean diameter as a result of an increasing ratio of centrifugal forces to drag forces. Finally, it should be mentioned that large carrier particles also exhibit good flow properties. They can be weighed easily and more reproducibly into capsules, blisters or metering locks of an inhaler device, although there is a limit to the size of the particles that can be entrained by the air or pass through capsule perforations (Steckel et al., 2004a).
1.3.2.3. The relevance of carrier payload

Carrier payload (drug concentration in the powder mixture) is one of the most relevant parameters in the drug-to-carrier interaction. Not many studies on the effect on the payload are known, even though in 1994 Timsina et al. mentioned that there was a lack of information (in the literature) about the optimum drug-to-carrier ratio. This lack of information becomes more relevant since highly potent anti-asthma drugs in very low dose ranges (e.g.: <20 µg) are currently being developed. Next to that, there is an increasing interest in pulmonary delivery of systemically active agents, like peptides and proteins (Niven et al., 1994; Patton et al., 1999), which may require high doses. Also high dose antibiotics have become interesting for dry powder inhalation, e.g. tobramycin and colistin in cystic fibrosis therapy (administered currently by nebulization in doses of 300 mg and 160 mg respectively). In this respect, it is surprising that most studies on adhesive mixtures for inhalation focus only on one single payload, most frequently 1.46% w/w (see Table 1).

Table 1: Examples of carrier payload applied in various studies

<table>
<thead>
<tr>
<th>Payload (% w/w)</th>
<th>Study</th>
</tr>
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<tbody>
<tr>
<td>0.05</td>
<td>Schlimmer, 2002</td>
</tr>
<tr>
<td></td>
<td>Dubois et al., 2003</td>
</tr>
<tr>
<td>0.2</td>
<td>Podczeck, 1998a, 1999</td>
</tr>
<tr>
<td>0.6</td>
<td>Harjunen et al., 2003</td>
</tr>
<tr>
<td>0.8</td>
<td>Young et al., 2002</td>
</tr>
<tr>
<td>1.0</td>
<td>Steckel and Müller, 1997</td>
</tr>
<tr>
<td>1.46</td>
<td>Kassem and Ganderton, 1990</td>
</tr>
<tr>
<td></td>
<td>Timsina et al., 1994</td>
</tr>
<tr>
<td></td>
<td>Zeng et al., 1998; Zeng et al., 2000a</td>
</tr>
<tr>
<td></td>
<td>Zeng et al., 2001b</td>
</tr>
<tr>
<td>2.0</td>
<td>Heng et al., 2000</td>
</tr>
<tr>
<td>2.5</td>
<td>Iida et al., 2001; Iida et al., 2003</td>
</tr>
<tr>
<td>3.2</td>
<td>Harjunen et al., 2003</td>
</tr>
<tr>
<td>5.0</td>
<td>Steckel and Müller, 1997</td>
</tr>
<tr>
<td>6.6</td>
<td>Harjunen et al., 2003</td>
</tr>
<tr>
<td>9.0</td>
<td>Steckel and Müller, 1997</td>
</tr>
<tr>
<td>10.0</td>
<td>Ikegami et al., 2000; Ikegami et al., 2003</td>
</tr>
<tr>
<td>11.1</td>
<td>Kawashima et al., 1998a</td>
</tr>
</tbody>
</table>

Like the carrier surface properties and size distribution discussed in the paragraphs 1.3.2.1 and 1.3.2.2, the role of the carrier payload may depend on the other parameters that influence the drug-to-carrier interaction. For instance, the drug concentration on the carrier surface has to be considered in relation to the drug bonding capacity of the active sites on the carrier. If such active sites are carrier surface discontinuities, there is an even more complex situation, because drug particles inside these discontinuities may find shelter from the previously
mentioned press-on forces during mixing. So, the drug concentration has to be considered in relation to the sheltering capacity of surface discontinuities too. But whether finding shelter from the press-on forces yields a higher fine particle fraction during inhalation (or not) depends also on the type of detachment forces, as explained in § 1.3.2.2.

Steckel and Müller, (1997) performed inhalation experiments with different payloads and three different carrier size fractions (from the same type of lactose). Their results did not clearly show an effect of these parameters on the fine particle fractions obtained, mainly because they used two inhalers with relative inefficient de-agglomeration principles. Harjunen et al., (2003) also investigated the effect of carrier payload on the (in vitro) deposition. However this study was focused primarily on mannitol and glucose carriers, whereas a wet suspension technique was used to prepare the mixtures. This must have influenced the drug-to-carrier interaction (compared to the commonly applied dry mixing).

1.3.2.4. The relevance of the drug properties

Many studies on adhesive mixtures for inhalation focus on the effect of the physico-chemical carrier properties. On the other hand, numerous studies have been reported regarding the effect of the physico-chemical properties of the drug on the drug-to-carrier interaction and the fine particle fraction obtained during inhalation. The type of drug (Price et al., 2002; Podczeck et al., 1995; Clarke et al., 2002), the drug particle size and drug concentration in the mixture (Kulvanich and Stewart, 1987), the drug crystalline habit (Song and de Villiers, 2004) and shape (Vidgren et al., 1987b; Larhrib et al., 2003a) have all shown influence the drug-to-carrier interaction.

Several techniques have been applied to prepare drug particles in the desired aerodynamic size range, for instance fluid energy milling (Lai et al., 1981). Special particle engineering techniques like supercritical fluid crystallization (SFC: Shekunov et al., 2003; Schiavone et al., 2004) have been used to produce drug particles with controlled surface characteristics, compared to ‘jet milling’ during which this cannot be achieved. It is claimed that particles prepared with SFC yield improved fine particle fractions compared to ‘standard’ micronized drug particles. Other particle engineering techniques, like spray-drying, supercritical drying and spray freeze-drying, have been applied to produce pulmonary drug particles for completely different reasons. Such techniques can also be used to produce particles in which for instance proteins are stabilized in the dry state by embedding them in amorphous sugars (so-called sugar glass technology) (e.g. Zijlstra et al., 2004; van Drooge et al., 2005). The same techniques can also be used to increase the ratio between geometric and aerodynamic particle size so as to avoid phagocytic clearance (so-called large porous particles technology, e.g.: Edwards et al., 1997) or to increase the dispersibility compared to micronized particles (PulmoSphere technology, e.g.: Duddu et al., 2002; Vanbever et al., 1999; van Drooge et al.,
Additionally, the preparation of hydroxy-propyl-methylcellulose phathalate nanospheres (Kawashima et al., 1998b), agglomerated drug crystals (Ikegami et al., 2000; Ikegami et al., 2003) and different salts of the same drug compound have been described (Jashnani and Byron, 1996). From the latter study, it was concluded that the type of salt used influences the hydrophilic/hydrophobic properties of the drug enhancing or decreasing its aerolization behaviour within an inhaler.

1.3.2.5. Ternary components in the powder mixture

Recently, ternary components, or so-called Force Control Agents (FCA) like isoleucine and magnesium stearate (Ganderton and Kassem, 1992; Colombo et al., 2000; Swaminathan and Kildsig, 2000; Young et al., 2002) have been incorporated into adhesive mixtures for inhalation. These ternary components have been shown to decrease the interaction force between drug and carrier particles, thereby enhancing the drug particle detachment during inhalation. It is claimed that these ternary components (partially) fill the active sites on the carrier surface before the drug particles can reach these places but also other mechanisms have been proposed. For instance, agglomeration between ternary components and drug particles may take place, which increases the detachment forces during inhalation (Louey et al., 2003).

1.3.2.6. The relevance of addition of lactose fines to the powder mixture

Apart from the previously mentioned ternary components, the presence/addition of lactose fines (generally < 10 µm) in adhesive mixtures has been recognised. Lactose fines may be present in adhesive mixtures due to wear (e.g. mixing or transport), the selection of lactose grades with wide size distributions (e.g. milled lactose grades (Karhu et al., 2000)), or from addition of lactose fines to coarser lactose fractions (Podczeck, 1998b; Zeng et al., 1998). It has been suggested that the effect of adding lactose fines to an adhesive mixture on the drug dispersion during inhalation may dominate over effects of carrier size and rugosity (Zeng et al., 2001b). It is likely that the addition of lactose fines enhances the drug particle detachment during inhalation in the same way as ternary components. However, there seems to be an optimum in the size and concentration of fine lactose as the ternary component for inhalation uses (Zeng et al., 1999; Adi et al., 2004). The role of fine lactose is far from understood, and more research will be needed to explain the effect of additional fines in combination with various carrier fractions and types of inhalers.

1.3.2.7. The relevance of mixing time and mixing intensity

In general, it is found that increasing the mixing time of adhesive mixtures increases the mixture stability and homogeneity. This seems logical, because increasing the mixing time also increases the time during which the press-on forces are enabled to increase the drug-to-carrier interaction forces during this process. It
also promotes drug re-distribution over the carrier surface from less active to more active bonding sites (de Boer et al., 2002c). These effects may result in a reduction of the drug detachment during inhalation. Which one of these effects is more pronounced, depends on the drug concentration in the mixture relative to the sheltering volume of the carrier surface discontinuities, respectively the binding capacity of the active sites again. It is thus surprising and disappointing that so few studies have been reported in which the effect of mixing time on the drug-to-carrier interaction in adhesive mixtures for the use in DPIs has been investigated (Zeng et al., 1999; Zeng et al., 2000b; Adi et al., 2004). In the few studies that have been reported, no attempts were made to correlate the mixing time (varying from 5 min to 90 min) or mixing intensity (varying from 20-150 rpm for a Turbula type mixer) with the outcome of inhalation experiments.

1.3.2.8. Interactions between the previously mentioned parameters

From the previous paragraphs it may be clear that the performance of adhesive mixtures for inhalation depends on many different parameters. It may also be clear that the effect of a single parameter could depend on the choices made for the other parameters that are known to influence the drug-to-carrier interaction and drug detachment during inhalation. Many interactions exist as well as several correlated effects. As a result, it is not only nearly impossible to study the complex effect of a variation in one single parameter without varying the others. Varying one parameter may even include changes in more than one respect. For example, changing the carrier size distribution changes the drug concentration on the carrier surface. But because carrier rugosity and carrier impurities vary with the carrier particle diameter (de Boer et al., 2003a), it also changes the number of drug particles relative to the bonding capacity of the active sites and the storage volume of the carrier discontinuities (de Boer et al., 2002c). This may give a rather unpredictable overall effect. Moreover, the flow properties of the carrier fraction may change, and by that, the magnitude of the press-on forces during mixing may be different. Therefore, it should be realized that previously supposed carrier surface effects, may at least partly have been a bulk effect in some studies (e.g. Zeng et al., 2001b), which needs further investigation. Considering all these interactions and interferences, it is disappointing to conclude that in most studies only one single parameter was varied and results were mostly discussed with a focus on this parameter alone, thereby neglecting the other parameters that were varied alongside the particular variation studied. Particularly the effects of the carrier flow properties (carrier bulk behaviour), carrier payload and type of detachment forces (inhaler design) have been underestimated so far. Only a few studies are known that focused on the combination of these parameters and the type and size of removal forces (de Boer et al., 2002c; Steckel et al., 2004b; de Boer et al., 2005a).
1.3.2.9. The effect of mixture storage and exposure to a high relative humidity

The drug-to-carrier interaction in adhesive mixtures may change with time (during storage) depending on the storage conditions (Broadhead et al., 1995; Maggi et al., 1999; Harjunen et al., 2003), and the effect appears to be dependent on the payload and carrier size fraction. Braun et al. (1996) showed for 2 strengths of disodium cromoglycate in formulations with various types of carrier particles, higher fine particle fractions from mixtures stored (for 27 days) at 33% relative humidity than for mixtures stored at 55% relative humidity when using an ISF inhaler for the in vitro deposition studies. Furthermore, it has been found that the relative humidity of the air during inhalation may influence the fraction of drug detached from the carrier crystals (Vidgren et al., 1989; Hindle et al., 1995; Jashnani et al., 1995; Jashnani and Byron, 1996). This observation can be explained by the effect of the humidity on the energy necessary to separate drug and carrier particles from each other (Price et al., 2002) (see paragraph 1.3.3). Obviously, extremely hygroscopic drugs (Vidgren et al., 1989; Maggi et al., 1999) and carriers (Berard et al., 2002) are more sensitive in this respect. Given the importance of having stable starting materials (drug and carrier particles) and formulations during storage, surprisingly few papers have appeared on this subject.

1.3.3. Measuring the adhesion forces in adhesive mixtures

The force of (drug-to-carrier) particle adhesion can be estimated from the force required for drug particle detachment from the carrier particles in adhesive mixtures (Zimon, 1982). Various techniques have been used to determine the interparticulate forces in adhesive mixtures and they can be divided into bulk detachment and single particle detachment methods. Bulk detachment techniques include centrifugation (Podczek et al., 1995, 1997), mechanical/air jet sieving (Staniforth et al., 1981; Iida et al., 2003; Flament et al., 2004), and impact separation (Concessio et al., 1998). Recently, atomic force microscopy (with or without a carrier or drug particle as probe) has been applied to determine the detachment force (or energy) of a single drug particle from a carrier surface (Louey et al., 2001; Begat et al., 2004). The results are highly dependent on the carrier surface roughness, and the temperature and relative humidity of the air to which the specimens were exposed during the experiments. It has been found that increasing the relative humidity increases the adhesive force between the drug and carrier particles (Podczek et al., 1996; Price et al., 2002; Tsukada et al., 2004), but the extent to which the force increases depends on the type of drug. Although the principle of atomic force microscopy is very accurate and highly reproducible, it has certain disadvantages. It provides only information on the spot and it is very difficult to find a representative or typical carrier surface (or to map the entire carrier surface). This may explain why such great differences in results have been obtained between different studies (Frijlink and de Boer, 2004). Moreover, it is impossible to study the effect of repeated pressing of drug particles against the
carrier surface (on the adhesive force) under circumstances that simulate the mixing process.

1.3.4. Balancing the adhesive forces in the mixture with the detachment forces during inhalation

The extent of drug particle detachment during inhalation in a dry powder inhaler depends on the magnitude and effectiveness of the detachment (de-agglomeration) forces generated in the inhaler relative to the adhesive forces (in the mixture). These detachment and adhesive forces need to be balanced to obtain a high powder homogeneity and stability on the one hand and a reproducible and high amount of drug particles detached from the carrier crystals during the inhalation manoeuvre on the other hand. Achieving this balance requires the understanding and controlling of all parameters that are known to influence the drug-to-carrier interaction in adhesive mixtures for inhalation. It also requires an effective inhaler and an understanding of the detachment forces generated by the particular inhaler. In Fig. 4, a scheme of the most relevant variables is shown. Each of the variables may include a number of different aspects, as has been explained in the previous paragraphs. Unfortunately, not all properties of the drug or carrier can be fully controlled. Both components of adhesive mixtures can have small variations in size distribution, particle shape or the amount and composition of the impurities. Neither can the conditions during processing and storage of the starting materials and the mixtures always be controlled to the extreme. In an attempt to understand the experimental results from studies in which various parameters were changed, a so-called Force Distribution Concept was introduced (de Boer et al., 2003a; Frijlink and de Boer, 2004). Some practical applications of this concept are given in this thesis.

1.4. In vitro methods to determine the efficiency of dry powder inhalers

A standard method to evaluate the performance of adhesive mixtures in DPIs is to measure the aerodynamic particle size distribution in the aerosol cloud from the inhaler. The apparatus most frequently used for this analysis are cascade impactors. Their principle of operation, classification of the aerosol cloud in mass fractions as function of the aerodynamic diameter by inertial deposition, has been extensively described by several authors (Hinds, 1982; de Boer et al., 2002a). A cascade impactor consists of a series of successive nozzles (above impaction plates) through which the aerosol from the inhaler is drawn with a fixed flow rate. The velocity of the airflow through the nozzles increases between successive stages due to a decrease in nozzle diameter (de Boer et al., 2002a). Particles entering a certain stage may be collected on the impaction plate depending on their aerodynamic diameter. Large particles will deposit but smaller particles with lower inertia may pass the stage. This principle of classification takes place on subsequent stages, but as the velocity increases, the cut-off diameter shifts to lower
aerodynamic diameters. The mass fractions of drug collected on the different stages are analyzed and expressed as a function of the experimentally derived cut-off diameters for the stages at the flow rate used for the experiment. Although cascade impactor analysis is still the most used method in inhalation studies, it has a number of major disadvantages. The procedures are time consuming and the principle lacks the possibility of full automation. Moreover, analysis is only possible for a narrow range of constant flow rates, and the aerosol can only be classified into a relatively small number of size classes.

Fig. 4: Scheme of variables that influence the fine particle fraction from a DPI (from Frijlink and de Boer, 2004).

Another method to determine the particle size distribution of an aerosol cloud is by means of laser diffraction analysis. The principle has already been used for the characterization of nebulizers since the 1980’s (Ho et al., 1986; Hurley et al., 1994), but only recently, laser diffraction has also been applied successfully for dry powder inhalers (de Boer et al., 2002b; de Boer et al., 2002c). The principle of laser diffraction is to pass the aerosol particles through a laser beam. The laser light is diffracted by the particles and the angle of diffraction depends on the particle diameter. Recording of the diffracted light on a series of concentric detector rings enables calculation of a volume distribution in the aerosol as function of the particle diameter from the complex diffraction pattern on these rings. For these calculations, a choice between the Fraunhofer and Mie diffraction theories has to be made. Although laser diffraction is fast and can be fully automated, there are some drawbacks to this technique as well. A frequently mentioned drawback is that particles are classified on their optical properties correlated to size instead of
measuring aerodynamic particle sizes and that volume distribution curves are calculated based on the assumption that the particles are spherical (de Boer et al., 2002a). For comparative evaluation, this is not really a problem however. For dry powder aerosols the primary particle size distribution of the drug can serve as a reference. A practical limitation of standard laser diffraction analysis is that no flow controlling system is available with which the aerosol can be drawn from the inhaler. Therefore, recently a special inhaler adapter has been developed for medical aerosol characterization (de Boer et al., 2002b).

In the studies presented in this thesis, investigation of the drug detachment from carrier crystals as function of different parameters was the main objective. Most conclusions were neither based on standard cascade, nor on standard laser diffraction results, alone. But for a few exceptions, all experiments were conducted with a special test inhaler with carrier retention in a classifier-like de-agglomeration chamber. The test inhaler was connected to a standard cascade impactor (Apparatus 3 as described by the European Pharmacopoeia 4th Ed. 2002) and retained carrier particles were removed from the classifier chamber and analyzed upon residual drug after inhalation. This residual drug is referred to as carrier residue (CR). Only as additional information, and for marketed DPI’s, fine particle fractions (FPF’s) collected in the impactor were analyzed. The reason for using CR rather than FPF for drawing conclusions about drug particle detachment during inhalation is the higher reproducibility of CR compared to FPF measurements, the latter is often subject to uncontrolled losses in the impactor (for instance due to tribocharge). Laser diffraction technique was particularly used to obtain more detailed information about the mode of drug particle detachment from the carrier crystals, e.g. as primary particles or as small agglomerates. This aspect cannot be studied with cascade impactors, as these devices are unable to discriminate between small agglomerates (with a relatively low density) and solid primary particles (with a much higher density) since both types of particles may have the same aerodynamic diameter.

1.5. Aim of this thesis

The studies described in this thesis are part of a larger research programme on pharmaceutical and technological aspects of pulmonary drug administration, that is carried out at the Department of Pharmaceutical Technology and Biopharmacy of the Groningen University in The Netherlands. Previous studies on adhesive mixtures for inhalation focused mainly on a few single aspects, being particularly carrier size, carrier surface impurities and rugosity (expressed as pores, clefts and adhering fines), carrier payload (amount of drug in the mixture) and the mixing time, without investigating the possible interactions between these parameters. Considering that carrier bulk properties and carrier surface properties both vary with the carrier size distribution, it must be clear that the effect of changing the carrier size distribution on the obtained fine particle fraction during
inhalation cannot solely be attributed to either of these parameters. Another parameter that is correlated with the carrier particle size is the carrier payload. The degree of significance for all of these parameters may depend on the mixing time and mixing intensity. Finally, to establish an optimal balance between the adhesive forces in the mixture and the removal forces during inhalation, the type of inhaler to be used for the experiments is relevant, as well as the inspiratory flow manoeuvre at which the inhaler is operated.

The major objective of this thesis is therefore to investigate the role and relevance of the different aspects (parameters) and their mutual interactions related to the carriers used in adhesive mixtures for dry powder inhalations. The studies aim to improve the understanding of the influence of (lactose) carrier surface and bulk properties on the drug-to-carrier interaction in dependence of carrier payload, mixing conditions and type of detachment forces generated during inhalation and their complex mutual interactions and dependencies.

A metal (earthed) test inhaler based upon air classifier technology proved to be a suitable tool for these investigations, since it turned out to be effective in drug particle detachment also when carrier particles with a high surface rugosity are used and it enabled the measurement of the amount (and location) of drug particles not detached from the carrier during inhalation (de Boer et al., 2003a). With the help of laser diffraction technique, also the mode in which drug particles were detached (as single entities or as small agglomerates) could be studied.
1.6 References


Chapter 1


Chapter 1


