1 Introduction

Inhalative application of drugs is used by mankind for millenniums and can be traced down to 2000 B.C. in India. Due to its parasympatholytic action, Atropa belladonna leaves containing atropine were applied as a cough suppressant by smoking [Labiris, N. R. et al., 2003]. Also in the 19th and early 20th century cigarettes containing stramonium powders were smoked for treatment of asthma symptoms [Anderson, P. J., 2001]. Generally, inhalative medication was very popular in late 19th century. Medications were put into boiling water and inhaled by the patients from special ceramic bottle like devices, the glass bulb nebulizers. Two basic types of nebulizers are currently in use today, jet and ultrasonic systems. Both nebulizers do not require special inhalation techniques. This easy to handle principle still makes them an excellent choice for infants and geriatric patients.

Still the invention of the chlorofluorocarbon (CFC) propellant driven pressurized metered dose inhalers (pMDI) was a major improvement for patients. The pMDIs are handy and portable tools, which deliver drugs with a high reproducibility if used correctly. However, most pMDIs do have some major disadvantages, like the complicated breathe-device coordination. Also the large size and high velocity of the generated droplets lead extensive impaction rates in the upper airways, which needs to be overcome by use of bulky spacer add on devices [Newman, S. P. et al., 2002]. The most prominent disadvantage is definitely the ozone harming effect in our atmosphere through the CFC propellants, which were part of most pMDIs formerly. In 1987 all CFCs were banned by the Montreal protocol, which triggered their replacement by the hydrofluoroalkanes (HFAs), HFA 134a and HFA 227. The substitution of CFC propellants by HFA propellants was followed by major changes in the drug formulations. For that reason pharmaceutical companies enforced a technology platform used for inhalative application before, the dry powder inhaler [Crowder, T. M. et al., 2001].

1.1 Dry powder inhalers

The first commercially available Dry Powder Inhaler (DPI) was in the 1940s the Aerohalor® from Abbott Laboratories, Abbott Park, IL (Fig. 1.1-1 I), which was used to deliver isoprenaline powder into the lungs. The Spinhaler® from Fisons Corp., Bedford, MA, was the first modern DPI and introduced in 1971. The Spinhaler®, a multi-dose device, uses hard gelatin capsules as drug reservoirs and is suitable to deliver up to 20 mg of drug with a multi-dose. Up to now several DPIs entered the market, especially in Europe. Basically there are two types of DPIs, passive and active. Both types work by the same principle and therefore show the same two major advantages. The first major advantage is that DPIs are generally breath controlled and do not require breathe-device coordination as pMDIs do. The second major advantage is the possibility of high dosing flexibility, which ranges from 6 µg to 20 mg or more active component per shot [Smith, I. J. et al., 2003]. DPIs always consist of four modules, the powder vessel, the metering and dosing system, the disintegrator and the mouthpiece. Active and passive DPIs only differ in the disintegration principle. The passive DPIs are available on today market either as multi-dose or multi-dose inhalers. The latter again must be divided into multiple unit dose inhalers and reservoir system inhalers. Single dose inhalers usually carry their unit-doses in capsules. Before each application the patient needs to place one capsule into the inhalator, where it gets either pierced, like in the HandiHaler® (Boehringer Ingelheim), or cut into two pieces by a dedicated mechanism, e.g. Rotahaler® (GlaxoSmithKline). In multiple unit dose inhalers, e.g. Diskhaler® (GlaxoSmithKline), the multi-doses are most commonly stored in multi-dose blisters within a multidose package. By opening the Diskhaler® lid the disk rotates, the new blister is pierced and ready for inhalation. There are also some capsule based multi-dose Inhalers, like the Inhalator® M from Boehringer Ingelheim which can carry up to six capsules. Also very common are the reservoir inhalators, like the Turbohaler® from AstraZeneca. Before inhalation the powder is stored in a container. For application the multi-dose is prepared for disintegration by volume-based metering unit. All passive DPIs mentioned above have in common, that the powder disintegration mechanism strongly depends on the patient and his inspiratory flow. Powder disintegration means either to brake up powder agglomerates into particles small enough to reach the lower airways or to separate the micronized pulmonary applicable drug particles from the

larger carrier particles (e.g. lactose). The patients inspiratory air flow needs to overcome the inhalers air flow resistance to generate the aerosol cloud by directing a turbulent air stream through the powder bed. Therefore increased lung deposition is achieved by high resistance devices [Labiris, N. R. et al., 2003].

Fig. 1.1-1 Abbott Aerohalor® (I) [www.inhalatorium.com]and Nektar Pulmonary Inhaler(II) [www.nektar.com]

In contrary, active devices incorporate an internal energy source, which liberates aerosolization and particle cloud generation completely from the patient inspiratory airflow. This recommends active DPIs as appropriate devices for children, geriatric patients and patients with a generally reduced inspiratory flow. The most prominent among the forthcoming active DPIs is the Nektar Pulmonary Inhaler (Nektar Therapeutics, San Carlos, CA, USA), which will be used as application device for Exubera®, the first pulmonary applicable insulin (Fig. 1.1-1 II). The device generates a ready-to-inhale standing cloud with compressed air. Right before inhalation the aerosol cloud is located in a transparent chamber, which allows the patient to rate inhalation efficiency by visual control [Bakshi, A. et al., 1999]. Another approach is the Spiros® Inhaler (Dura Pharmaceuticals, San Diego, CA, USA) which uses a battery driven propellant for powder dispersion [Han, R. et al., 2002]. In summary active DPIs are very promising application devices for the future although until today no active DPI entered the market. Active DPIs liberate the delivered dose from the patient inspiratory air flow and increase dosage reproducibility.

1.1.1 Classical pulmonary powder formulations

In contemporary DPI formulations usually very small amounts (3 µg to 500 µg) of classical small - molecule active agents have to be applied for correct medication. As the particle size distribution of the delivered drug also needs to be very low (1 to 5µm) the flow properties of the pure active agent powders are very poor, due to large van der Waals forces. Therefore and to facilitate dose metering two types of formulations are used today in DPIs.

The “inhalative pellets” are built by aggregation of many micronized drug particles. The binder agent free aggregates show significantly improved flow properties. During the inhalation, the pellets are broken to smaller pieces again by the DPI disintegration unit. The particle size distribution of the resolving smaller aggregates or primary drug particles is suitable for deep lung delivery. Pellets are used predominantly in Turbohaler® (AstraZeneca) formulations [Newman, S. P. et al., 2002]. Traditionally DPI formulations are blends of large carriers and micronized drug particles. They form adhesive or interactive mixtures by attaching the micronized drugs to the surface of the carrier. The coarse carrier material is predominantly crystalline α-lactose monohydrate with particle sizes of 50 to 200µm. By inhaling the formulation, the micronized drug particles are detached from the coarse carrier surface and aerosolized. The fine aerosol is delivered to the deep lung. The large carrier crystals deposit by impaction forces in the throat. Local side effects occur quite often due to incompletely detached drug particles [Koning, G. A. e. a., 1999].

Factors influencing optimal drug carrier formulation were objective of numerous studies. A number of authors varied carrier size and drug to carrier ratio in order to increase pulmonary delivery of micronized drugs. Braun et al. examined the deposition of disodium cromoglycate and found that a drug to carrier mass ratio of approximate 1:1 combined with small sized carriers achieved best values for deposition in impingement chambers [Braun, M. A. et al., 1996]. Steckel et al. investigated the effect of lactose carrier particle size and budesonide concentration in binary mixtures. They found for that small sized carriers in combination with low drug load resulted in the highest fine particle fraction [Steckel, H. et al., 1997]. Tee et al. examined different carriers for micronized salbutamol sulphate particles and found a decreasing in drug aerosolization

order of mannitol > sorbitol > lactose [Tee, S. K. et al., 2000]. Another major issue for pulmonary drug delivery efficiency is the effect of carrier particle shape and surface rugosity. The influence of differences in surface roughness of lactose carriers on the emitted dose and delivered fine particle fraction of prankulast hydrate was investigated [Kawashima, Y. et al., 1998]. Lactose carrier particles with high surface roughness emitted effectively from the delivery device, but showed a reduced fine particle fraction due to stronger adhesion of drug particles to the carrier surface. Spray-dried amorphous and smoothed lactose carrier particles only slightly improved inhalation efficiency, since still fairly strong drug carrier adhesion forces were present: In contrast spray-dried crystalline particles with low wrinkled surface strongly increased inhalation efficiency. The deposition may also be affected by the amorphous and crystalline nature of the particles, since amorphous particles are in a higher energetic state. In another detailed study the effect of morphology and surface rugosity of crystallized lactose carriers with nearly identical particle size distributions on the aerosol efficiency of micronized salbutamol sulphate was investigated [Zeng, X. M. et al., 2000]. Both, increase in surface smoothness and elongation ration, the ratio of particle length versus particle width, improved fine particle fraction and drug dispersibility independent of the delivery device. The positive effect of elongated particles is in good agreement with previous findings, where elongated particles showed markedly lower aerodynamic diameters than spherical particles with similar volume or mass [Hickey, A. J. et al., 1992]. The authors postulated that more elongated lactose carrier particles travel a longer distance during inhalation before impaction occurs and adhered drug particles are subjected to the drag forces of the air steam for a longer period of time. This again would result in more drug particles being detached from the carrier surface, leading to higher fine particle fraction of the drug. In 1996 Staniforth and coworkers invented the ternary mixtures by adding leucine as an additive to the lactose carrier – drug blend [Staniforth, J. N., 19960808]. They assume that the most wrinkled sites of coarse carrier particles like lactose are areas with high surface energy. For that reason the drug particles in binary DPI blends preferentially attach to the sites of high surface energy. Therefore, drug distribution on the carrier surface is inhomogeneous on one hand and drug disintegration from the carrier surface is less likely and incomplete on the other hand. By previous addition of inherent additives like leucine, fine particle lactose, PEG

[Lucas, P. et al., 1998] or magnesium stearate (Powderhale®, Vectura, UK) the active sites are already occupied by the additive before the drug is added to the blend. In the complete formulation drug disintegration and thereby deep lung delivery of the active compound is significantly improved. Blends of micronized drug, fine particle lactose and an ultra low density additive, namely spray-dried leucine, is the consequent further development of the ternary mixtures [Lucas, P. et al., 1999]. Tee et al. confirmed these findings for above mentioned binary mixtures of salbutamol sulphate and coarse carrier mixtures. Addition of jet milled mannitol, sorbitol or lactose fine particles forming ternary mixtures improved aerosolization behavior significantly [Tee, S. K. et al., 2000]. All these results confirm that appropriate selection and (pre-) conditioning of carriers, concerning their particle size distribution, shape and surface properties, combined with ideal drug to carrier ratios leads to dry powder formulations with optimized pulmonary drug delivery efficiency.

1.1.2 Innovative pulmonary powder formulations

Most conventional DPI Formulations described above comprise a blend of micronized drug particles and coarse carriers and are therefore limited in their absolute drug load. The pulmonary application of biopharmaceuticals often requires higher drug loads combined with distinct dosage reproducibility. Therefore, more sophisticated carrier free formulations would be helpful to meet the requirements. In 1997, Edwards et al. published data on inhalation of large porous particles, which is the fundament of the Alkermes AIR® technology. The AIR® particles have mass densities less than 0.4 g/ml and therefore relatively large geometric diameters of 5 to 30µm, but the desired small aerodynamic diameters of 1 to 5µm [Edwards, D. A. et al., 1997]. This results in respectively high amounts of deposited particles in the deep lung [Vanbever, R. et al., 1999b]. Compared to particles with similar aerodynamic behavior, the relatively large AIR® particles show significantly superior flow properties and therefore need less energy for dispersion. The natural lung clearance mechanism is also delayed, since the particles are simply too big to be opsonized by the macrophages [Edwards, D. A. et al., 1998]. Alkermes claims that AIR® particles are suitable for small molecules, peptides,

proteins or generally spoken all macromolecules. Since there is no need to add carrier molecules to improve powder dispersibility drug loads from 1 to 90% are possible.

Dellamary et al. described in 2000 a two step process for the production of pulmonary applicable hollow porous particles with characteristics similar to the AIR® particles [Dellamary, L. A. et al., 2000]. The PulmoSphere® particles are generated by spray-drying an emulsion containing perflubron as a blowing agent and phosphatidiylcholine as the principal excipient. The particles are suitable for application of small molecule drugs in pMDIs [Hirst, P. H. et al., 2002] and DPIs [Duddu, S. P. et al., 2002]. The PulmoSphere® technology was developed by Alliance Pharmaceuticals and is now property of Nektar Pharmaceuticals intellectual property portfolio.

Chew and Chan compared wrinkled with smooth and spherical BSA particles on their in vitro inhalation performance using a Dinkihaler® device [Chew, N. Y. K. et al., 2001]. Although, apart from morphology related properties (specific surface, envelope density), both particle populations had similar solid-state characteristics (particle size distribution, residual moisture, true density, amorphousness) the solid corrugated BSA particles showed superior inhalation performance. The authors refer the different behavior to the reduced true area of contact between the particles, and thus reduced cohesiveness [Chan, H. K. et al., 2003].

Technospheres®, developed by Mannkind Corporation (formerly The Pharmaceutical Discovery Corporation), is a sophisticated dry powder formulation for the pulmonary application of insulin [Pfutzner, A. et al., 2002; Steiner, S. et al., 2002]. Insulin and a diketopiperazine-derivative enhancer self assemble into ordered lattice arrays at low ph. Subsequent lyophilization results in particles with 2 to 4µm diameter, which are suitable for pulmonary delivery by a capsule based passive DPI device. The inhaled particles dissolve at neutral pH in the alveoli and release the insulin rapidly, resulting in 50% bioavailability. Although initial results with the Technosphere® insulin formulation are encouraging, the use of absorption enhancers must be evaluated carefully to ensure long-term safety [Owens, D. R., 2002].

The examples illustrate the major impact of innovative formulation development on the performance and therefore pharmacodynamic and pharmacokinetic effects of pulmonary applicable powders. Some of these sophisticated formulations will for sure find their

place in new and challenging fields as the application of biopharmaceutical agents like peptides and proteins.

1.2 Deep lung delivery of biopharmaceuticals

The advancement in gene- and biotechnology changes medication dramatically. New biological entities with high specificity and selectivity entered the market in the past decade. EPO, GCSF, interferons and interleukins are successful heralds of dozens of new biopharmaceutical drugs awaiting official approval within the next years. Protein drugs represent one of the fastest growing markets within pharmaceuticals. In 2002 protein drugs market volume already reached $33 billions without insulin, and is expected to reach $71 billions in 2008 [Robert Cyran, 2004].

Nevertheless, until today most approved macromolecule formulations are delivered by parenteral application routes, predominantly via intravenous, subcutaneous or intramuscular injection. Parenteral drug administration is often not very well accepted by the patients, in particular because most indications for the use of macromolecular agents demand long-term treatment. This leads to low patient compliance and an increase of therapy costs. In a survey with 40 diabetic patients, 75% of the patients reported anxiety about performing injections when insulin therapy was prescribed [Bashoff, E. C. et al., 1995]. Another study reports that 25% of diabetics miss their required injections [Weissberg-Benchell, J. et al., 1995]. Therefore, formulation scientists try engineering alternative application routes for macromolecules. Peroral, buccal, sublingual, intranasal, transdermal and also rectal application routes have been extensively tested by many researchers and may be promising for the future, but until now they show poor bioavailability and low reproducibility [Owens, D. R., 2002]. An application study of six polypeptides with molecular masses ranging from ~3.5 to ~20 kDa compared pulmonary with intranasal and enteral application routes and proved the superiority of the pulmonary to the other alternative application routes. The best intranasal bioavailability of ~6% was achieved for the smallest compound, human calcitonin, and best enteral bioavailability for parathyroid hormone 1-34 fragment was even lower with ~1.5%. Pulmonary bioavailability for all macromolecules was significantly higher, e.g. ~36% for human calcitonin [Mackay, M. et al., 1994]. These findings were confirmed and complemented by Patton et al., who also found relatively