

Chapter 3

The relevance of solid state properties of aminoglycoside antibiotics to dry powder dispersion in a DPI

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Abstract

Aminoglycosides are scarcely absorbed via the gastro-intestinal tract, and for that reason they are often administered by injection, which is an invasive administration technique. Tobramycin for the treatment of pulmonary infections is currently also nebulised after early inhalation studies with this drug in the 1980s showed promising results against *Pseudomonas aeruginosa* in Cystic Fibrosis patients. However, nebulisation has many disadvantages. The technique is ineffective, laborious and time-consuming and, thus, a burden to the patient. Dry powder inhalation may be a suitable alternative administration method for this type of drug, but in contrast with many other high dose drugs aminoglycosides have rather inappropriate properties for inhalation. Moreover, it is relatively unknown which, and to what extent, solid state and particle properties of the aminoglycosides (e.g. tobramycin, kanamycin and amikacin) are relevant to dispersion and device retention during inhalation. To make inhalation as dry powder feasible aminoglycoside antibiotics are often particle engineered to increase the consistency of delivered fine particle dose. However, many engineered inhalation particles contain relatively high amounts of excipients and this may significantly increase the amount of powder to be inhaled. In addition, the processes with which they are manufactured are frequently complex, involving a series of successive unit operations, which makes the powders expensive and vulnerable to batch variations. Therefore, our aim was to investigate whether pure aminoglycosides can be used as inhalation powder in an adapted inhaler design by selecting the most appropriate physical form (spray dried or micronised), salt or base and water content. For design and development of the dry powder inhaler, we selected tobramycin as a model compound. Tobramycin can be purchased either as free base or as sulphate salt of which the latter has a significantly higher molecular weight, which increases the powder dose to be inhaled. In this chapter, it is shown that the salt and the base, as well as different forms of the base, display different moisture sorption behaviour. The conclusions of this chapter are that spray dried tobramycin free base seems to be the most suitable candidate for pulmonary administration as pure drug without excipients. We also consider a disposable DPI most appropriate for hygroscopic aminoglycosides (and pulmonary antibiotics in general), to prevent that bacterial resistance development in the drug administration occurs and that retained particles absorb moisture and disturb following administrations.

General introduction

Various studies have shown that the physico-chemical properties of the drug or drug formulation strongly influence the dry powder aerosol generation process during inhalation [1, 2]. However, it is relatively unknown to which extent various solid state and particle properties of pure drugs like tobramycin, kanamycin and amikacin are relevant to dispersion and also inhaler retention. This may be particularly important information for the choice or development of the inhaler principle to be used. Most studies in the scientific literature focus particularly on changing the particle properties to obtain good dispersion in already marketed inhalers [3]. This frequently involves the use of (high amounts of) excipients and complex particle engineering processes of which the disadvantages have extensively been discussed before and in chapter 7 [4]. The focus in such studies is mostly on modifying the particle density and surface structure (rugosity) to improve dispersion by lowering the particle coordination number and the surface area per contact point. Complex particle engineering may not be necessary however, when a better understanding is obtained of how the solid state particle properties interact with the design of the dispersion principle and the type of forces generated in that principle during inhalation. This may result in development of new inhaler types of which the design is adjusted to the solid state properties of the pure drugs. The aim of this chapter is to discuss which solid state properties of aminoglycosides seem most relevant to dispersion, whether and how their influence can be changed to improve dispersion, and which techniques may be useful to study the dry powder aerosolisation behaviour of this class of antibiotics, with a focus on tobramycin.

Aminoglycosides introduction

Aminoglycoside antibiotics are therapeutic agents that display concentration dependent bacterial activity against most aerobic Gram-negative bacteria. They require a short contact time and are most effective against rapidly multiplying bacteria that are susceptible to the drug [5]. In spite of their wide use, their exact mechanism of action is still not completely known. Binding to the bacterial 30S and 50S ribosomal subunit, inhibiting the translocation of the peptidyl-tRNA from the A-site to the P-site, as well as misreading of mRNA have been reported. This leaves the bacterium unable to synthesize proteins that are vital to its growth [6, 7], but additional mechanisms on the bacterial cell membrane, explaining their bactericidal activity, are suspected as well [8]. Aminoglycosides of natural origin are isolates of bacteria of the *Streptomyces* or *Micromonospora* genera and named with the suffix mycin

or micin, respectively. Streptomycin was the first aminoglycoside isolated (in 1943) from *Streptomyces griseus*. It was also the first antibiotic used effectively against *Mycobacterium tuberculosis* (*Mtb*) in 1946 [9]. Gentamicin and tobramycin were discovered more than 20 years later and appeared to be particularly effective against *Pseudomonas aeruginosa* (*Psa*), which made them of interest for the treatment of pulmonary infections as in CF patients [10-13]. Workers of Eli Lilly isolated tobramycin in 1967 from the aminoglycoside antibiotic complex nebramycin as nebramycin factor 6, produced by a strain of *Streptomyces tenebrarius* [14]. This nebramycin complex consists primarily of tobramycin carbamate, kanamycin C carbamate and apramycin [11]. Tobramycin and kanamycin carbamates can be hydrolysed into the active forms tobramycin and kanamycin B. Both antibiotics are difficult to separate completely from each other however, as they differ by only one hydroxyl group. Amikacin (first synthesised in 1972) is a derivative of kanamycin A and has the widest antimicrobial spectrum of all aminoglycosides [7]. Because of structural differences resulting from the derivatisation process, amikacin is not inactivated by common enzymes that inactivate tobramycin and gentamicin. Therefore, amikacin is often used against drug-resistant bacteria [15]. Gentamicin, kanamycin A, and amikacin are second-line antibiotics used to treat (multidrug-resistant) tuberculosis (TB). Other more recently isolated aminoglycosides could be interesting for pulmonary administration as well, but this chapter focuses primarily on their (general) properties as a dry powder for inhalation and not so much on the different types and their applications.

Because aminoglycosides are scarcely absorbed via the gastro-intestinal tract, they are often administered by injection which is an invasive administration technique. This stimulated the search for alternative routes of administration. Agents like gentamicin and tobramycin, used to treat pulmonary infections caused by *Psa* in cystic fibrosis (CF) and non-CF bronchiectasis patients, are currently often nebulised for inhalation after early nebulisation studies with these drugs in the 1980s showed promising results [13, 16, 17]. Inhalation for the treatment of pulmonary infections has the advantage that the drug is delivered directly to the site of action which increases their local concentration, even for lower doses compared to systemic delivery. It also reduces the severe adverse systemic side effects of aminoglycosides [18]. However, nebulisation has many disadvantages, as described in the chapters 1, 4 and 7 of this thesis, and this opened the way for dry powder inhalation. Studies with tobramycin sulphate (TOBI[®], Novartis), developed using PulmoSphere[®] technology and approved by the FDA in 2013, showed that the dry powder formulation has a safety and efficacy profile comparable with that of the tobramycin solution and improves patient

convenience and satisfaction [19]. Therefore, replacing wet aerosolisation by dry powder aerosol generation has eliminated many drawbacks of pulmonary administration. Also powder formulations for inhalation of the aminoglycosides gentamicin and amikacin have been presented [20, 21], although most efforts have been focussed on tobramycin [1, 22-25]. Many of these studies have been reviewed by Traini and Young [26]. Because tobramycin is the most widely used inhaled antibiotic in CF treatment [17], this chapter focuses particularly on this aminoglycoside antibiotic.

Chemistry and solid state properties of aminoglycosides

Aminoglycosides are natural or semisynthetic compounds of which the name is derived from their chemical structure made up of amino groups ($-NH_2$) attached to glycosides (derivatives of sugar). Most aminoglycosides (e.g. kanamycin, tobramycin, dibekacin, gentamicin, sisomicin and netilmicin) have very similar chemical structures, comprising three carbohydrate units. They differ in one or two functional groups, mostly a hydroxyl (OH) or methyl (CH_3) group, except for streptomycin, the semisynthetic amikacin and the neomycins. For instance, kanamycin A differs from tobramycin only by one hydroxyl group and the exchange of a hydroxyl group by an amino radical (NH_2) (Figure 3.1) and therefore, this compound may physically have similar properties. Amikacin, being a semisynthetic derivative of kanamycin A, is also considered interesting in the treatment of CF patients, but it may have different properties due to the acylation with L(-)- γ -amino- α -hydroxybutyric acid at the C-1 amino group of the 2-deoxystreptamine moiety [27].

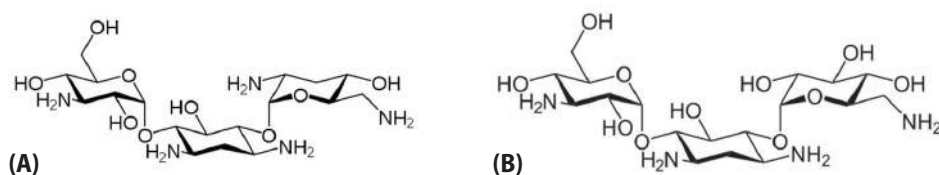


Figure 3.1 Structures of tobramycin (A) and kanamycin A (B).

Aminoglycosides are available as free base or as salt. Different forms and salts may be produced to improve certain physical and/or chemical properties like the solubility or the hygroscopic nature of the compound. Also patient acceptance and tolerance may depend on the type of salt used as has been shown by Westerman et al. for colistin [28].

The sulphomethate sodium of this drug was much better tolerated than the sulphate salt. For tobramycin the salt is mostly sulphate; amikacin and kanamycin are also available as disulphate. Tobramycin ($C_{18}H_{37}N_5O_9$), having a molecular weight of 467.52 g/mole in the anhydrous state, can be purchased either as free base or as sulphate salt ($(C_{18}H_{39}N_5O_{13}S)$ or $[2(C_{18}H_{37}N_5O_9)_2 \cdot 5(H_2SO_4)]$) of which the latter has a molecular weight of 1425.45 g/mole and contains only 65.6% of the free base) [29]. The free base is reported to exist also as a monohydrate, a dihydrate or a trihydrate [30], corresponding with 3.71; 7.15 and 10.35% water of crystallisation, respectively. Aminoglycosides are extremely hygroscopic materials and they may contain substantial amounts of water of absorption too [22]. Tobramycin is highly soluble in water and is stable when in solution at pH 1–11 and temperatures between 5 and 37 °C [12].

The solid state properties on a molecular level are partly determined by the arrangement of the molecules. This arrangement determines whether the solid exists in the crystalline state, has amorphous fractions or is completely amorphous, or whether hydrates are formed. These properties influence, for instance, the solubility and hygroscopicity of the powder, but also its stability, or its adhesive/cohesive nature which all can have an effect on the inhaler performance. Techniques that can be used to characterise the solid state properties are Dynamic Vapour Sorption (DVS), Scanning Electron Microscopy (SEM), Powder X-Ray Diffractometry (XRPD), Differential Scanning Calorimetry (DSC), thermographic analysis (TGA) and spectroscopic methods like solid state nuclear magnetic resonance (NMR) or raman and near infrared Fourier transformed infrared (FTIR). Figure 3.2, as an example, compares the water sorption of different tobramycin forms determined at room temperature. The figure shows that there is a considerable difference in the moisture sorption between the (spray dried) sulphate and the free base. For the sulphate (TOB sulphate SD) it was observed that the particles comprise a dry powder when they are in equilibrium with a relative air humidity (RH) of less than 30% (Figure 3.3A). At a water content of maximally 8–9%, the particles have a strong tendency towards agglomeration, but they can still be dispersed into primary entities [31]. However, when the RH is increased liquid layers are formed around the particle surfaces by moisture sorption which makes them sticky and gives rise to capillary condensation. At further increase of the RH to a value above 50% (Figures 3.3B and C) the particles start dissolving in their water of absorption, thus forming a highly viscous syrup which is diluted when the RH-value is further increased.

Surprisingly, the spray dried TOBI® formulation shows the same behaviour as the spray dried sulphate (Figure 3.2). Apparently, the formulation with 1,2-distearoyl-sn-glycero-3-

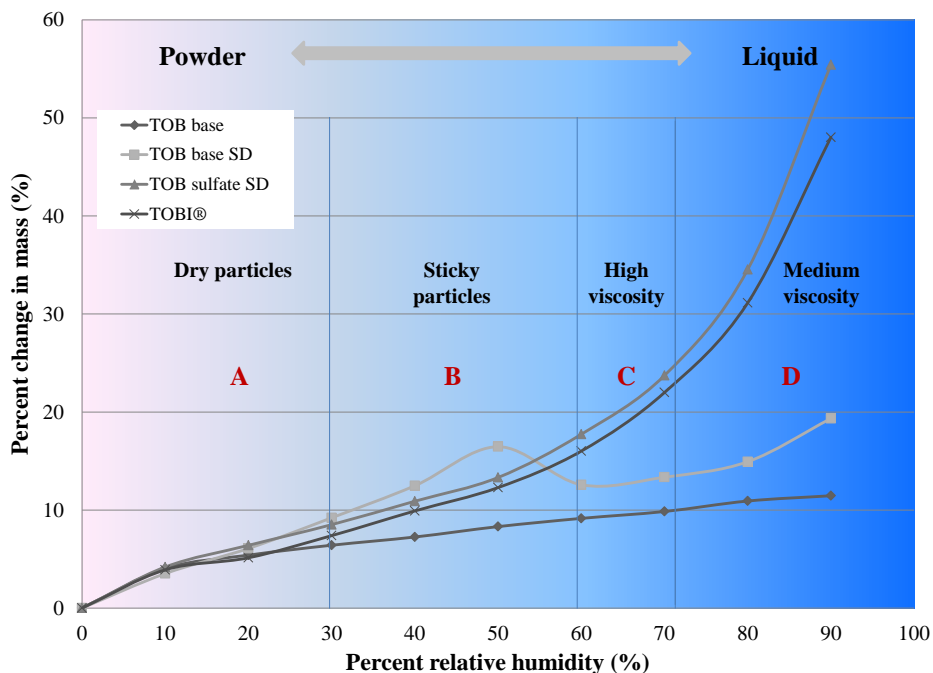


Figure 3.2 Moisture sorption isotherms of tobramycin as crystalline free base (TOB base), as spray dried free base (TOB base SD), as spray dried sulphate (TOB sulphate SD) and as sulphate in the marketed tobramycin powder for inhalation (TOBI®). A, B, C and D indicate the regions where spray dried tobramycin sulphate powder is present as dry particles, sticky particles, fused particles and dissolved particles, respectively.

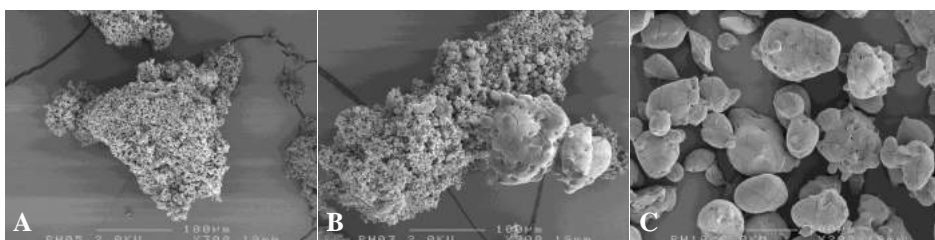


Figure 3.3 Scanning electron micrographs of crystalline tobramycin base after exposure to a maximum relative humidity (RH) of: (A) 30% RH; (B) 50% RH; (C) 70% RH. Dissolved and coalesced droplets have become solid particles during specimen preparation (C).

phosphocholine (DSPC) does not change the moisture uptake of the antibiotic although, in contrast with pure spray dried sulphate, fusion of particles as shown in Figure 3.3 does not occur [32].

Tobramycin base in Figure 3.2 shows a completely different moisture sorption isotherm. The crystalline product, which is probably a monohydrate [30], exhibits a very slow moisture

uptake between 10 and 90% RH after a much higher initial uptake of 4% between 0 and 10% RH which is comparable to that of the sulphate. After spray drying, yielding an amorphous modification, the higher initial moisture sorption is continued till 50% RH, reaching a maximal value of 16.5%, followed by a drop in water content between 50 and 60% RH to only 12.6%, and again an increase between 60 and 90% RH to an end value of 19.3%. This suggests that between 50 and 60% RH a trihydrate is formed [30], which binds 10.35% of water, after which the excess of water is temporally expelled. Because the RH value is meanwhile increased, the total water content at 60% is higher due to ongoing adsorption on the particle surface. The difference between the spray dried and crystalline base may be explained by the difference in mean particle diameter, which for the spray dried product is much smaller than for the crystalline base.

The much lower water content of the free base at the same RH than the sulphate, makes the base much more appropriate for inhalation. The free base, which is the active material, also has a much lower molecular weight, meaning that the inhaled powder dose can be reduced to 65.6% compared to the sulphate. Furthermore, the water sorption of tobramycin should be taken into account when the packaging material, packaging conditions, and the type of dry powder inhaler (DPI) are selected. The hygroscopic nature of tobramycin is a risk for good dispersion when a used DPI is stored at high RH and powder residues in the inhaler absorb moisture from the air to become sticky or even liquefied (Figure 3.3). A disposable device is therefore recommended for dry powder tobramycin administration and that of aminoglycosides more in general.

Physical particle properties relevant to dry powder inhalation

The chemical (or solid state) drug properties, discussed in the previous paragraph, in combination with the physical particle properties determine the powder (bulk) behaviour of the drug. The physical particle properties relevant to powder behaviour are well known and include particle shape and size distribution, particle density and surface texture, including rugosity. During inhalation particle properties and powder behaviour are relevant with respect to emptying of the dose compartment, dispersion into a suitable aerosol for inhalation and retention in the inhaler device. Partly, these properties can only be varied within very narrow limits. For instance, as already discussed in chapter 1 of this thesis, aerosols for inhalation should contain the drug particles in the correct aerodynamic size distribution for deposition in the desired target area which for antibiotics often is the

whole lung. Several studies have shown the effect of particle size distribution (PSD) and the inhalation manoeuvre with which the aerosol is inhaled on the deposition behaviour in the human respiratory tract [33, 34]. To reach the whole lung effectively, particles in the approximate size range between 1 and 5 micron have to be inhaled at a moderate flow rate (30–60 L/min). Particles smaller than 1 micron will substantially be exhaled again, whereas particles larger than 5 micron will deposit in high mass fractions in the oropharynx. It is well established that the PSD is one of the most significant factors to affect flow behaviour of powders [35]. Small particles have a high ratio of surface area to volume which causes interparticulate attractive forces to dominate over the force of gravity and resist bulk flow when a shear is applied to the powder. As a rule of thumb it is generally accepted that particles > 100 μm have good flow properties. Diameters of particles in the appropriate range for inhalation are much smaller and such particles are, therefore, not free-flowing. Possible consequences of that are discussed in the paragraph powder properties relevant to dry powder inhalation.

By definition only sedimentation is the appropriate technique for measuring the aerodynamic size distribution, as the aerodynamic diameter of a particle is the diameter of a unit density sphere having the same terminal settling velocity in still air as the particle in consideration. By expressing the particle's terminal settling velocity either in terms of its aerodynamic diameter (D_A) or its equivalent volume diameter (D_E), the aerodynamic equivalent can be computed from equating both expressions, yielding:

$$D_A = D_E \cdot (\rho/\chi)^{0.5} \quad \text{Eq. 3.1}$$

where ρ is the particle density and χ is the particle's dynamic shape factor [36].

Practically, for aerosol characterisation from inhalers, cascade impactor analysis can be used as a suitable alternative, yielding mass fractions of aerosol as function of the aerodynamic diameter. Cascade impactor analysis is laborious and time consuming however, and for inhaler and formulation development laser diffraction technique yields much faster, also more accurate and very detailed information [37-39]. Although laser diffraction measurements do not produce aerodynamic size distributions, the technique has practical value because the size distribution of the primary drug particles is compared with that of the particles in the aerosol from the inhaler-formulation combination using the same measuring principle. From this comparison, the dispersion efficiency of the combination can be derived. For most solid drug particles, laser diffraction diameters can nevertheless

approach aerodynamic diameters when the particles are solid, having a density between 1 and 1.5 g/cm³, and are slightly irregular, having a dynamic shape factor within the same range (1 to 1.5), which renders the term $(\rho/\chi)^{0.5}$ a value close to 1. Hence, the particle's equivalent volume diameter (D_E) approaches the aerodynamic diameter (D_A) in Eq. 3.1. In many studies, highly porous particles are produced however, in order to improve their aerosolisation behaviour [40–42]. Such particles have a very low density (ρ), which enables to increase their geometric size while maintaining their small aerodynamic diameters. Such so-called large porous/hollow particles experience the same interparticulate forces as much smaller high density particles, as they have the same mass, whereas dispersion forces of the drag and lift type acting on such particles during inhalation are much higher. Alternatively, or additionally, particle shapes and/or surfaces can be altered to reduce the interparticulate forces. Irregularly shaped particles create higher bulk porosities in the powder due to deteriorated flowability and packing. This results in a lower coordination number (number of contact points) per particle. Particle surface rugosity, or surface porosity, may reduce the size of a contact area, having the same positive effect on the interparticulate forces as irregular particle shapes [43, 44]. Properties like shape and rugosity can be investigated with SEM and image analysis (e.g. QicPic, Sympatec).

The top down and bottom up principles used to control particle size, as well as the particle engineering techniques utilised to modify particle shape, surface porosity and rugosity have extensively been described before [22, 25, 45–48]. Particle engineering frequently includes the addition of high amounts of excipients of which the disadvantages have been explained and discussed in the chapters 1 and 7. An example of engineered particles of tobramycin sulphate (TOBI®) with 37% excipients is shown in Figure 3.4A in comparison with spray dried (B) and micronised (C) tobramycin base without excipients. Although the crystalline state (obtained from micronisation when the starting material is crystalline too) is the most stable state, we selected spray drying as the preferred preparation technique for aminoglycosides, yielding amorphous particles. The shape, density and surface texture of amorphous aminoglycoside particles appear to be more suitable for dispersion as a dry powder in air classifier based DPI than that of micronised particles, whereas the stability of both particles is more or less the same (Figure 3.2). Aminoglycosides are highly hygroscopic by chemical nature and their physical state does not change much to that, in contrast with many other compounds.

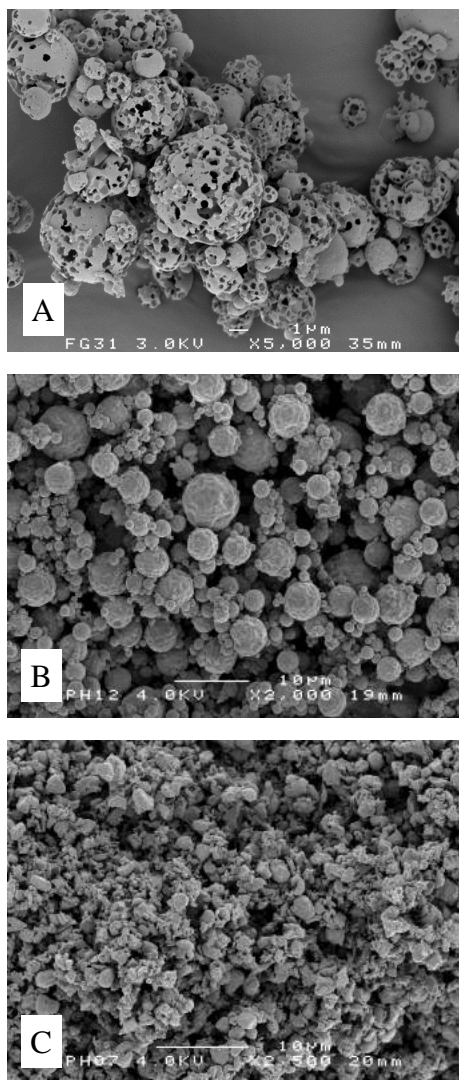


Figure 3.4 Scanning electron micrographs of TOBI® Podhaler™ formulation (A); pure spray dried tobramycin base (B) and pure jet milled tobramycin base (C).

Powder properties relevant to dry powder inhalation

The underlying factor of importance for various steps in the entire process of pulmonary drug delivery as a dry powder is the flowability of the powder. It starts with the filling of the dose compartments during inhaler production. Poor flowability may result in dose variation and special filling equipment, or controlled agglomeration may be necessary

to obtain the desired consistency of weighed dose. For low dose drugs agglomeration is mostly in so-called adhesive mixtures where coarse free flowing crystals host the micronised drug particles on their surface [49-51]; for high dose drugs agglomeration is generally into soft spherical agglomerates [52]. During inhalation the dose compartment has to be emptied, either by entrainment of the powder in the inhaled air stream or by air flow induced spinning or vibration of the dose compartment, which is often a capsule. Various studies have shown that flow properties play a crucial role in powder entrainment from the dose compartment and dispersion [53, 54]. As mentioned in the previous paragraph, powder flowability is directly related to the interparticulate forces which are a function of the chemical nature, crystal habit and the particle properties of the drug. The same (cohesive) particle-particle forces also control the dispersion of dry powders into aerosols and the deposition (retention) in the inhaler device by particle-wall contact (adhesion). The nature of these forces is well understood and they can be distinguished into Van der Waals, electrostatic and capillary forces [55]. Preferably electrostatic interactions are to be avoided as they are poorly controlled and although they are mostly temporary, they can increase Van der Waals forces permanently. The existence of capillary forces (liquid bridges) depends on the chemical nature and physical state, as well as on the RH to which the powder is exposed. In general, RH-values higher than 65% are to be avoided [55], but for aminoglycosides (tobramycin) 40–50% is already too high. Not only are capillary forces quite strong, sometimes several times the mass of the individual particles when the vapour pressure of the surrounding air approaches the saturation pressure. They can also change into solid bridges upon temperature changes of the powder by crystallisation of dissolved drug after evaporation of the water of condensation in the capillaries.

To overcome the interparticulate forces during inhalation the dispersion forces derived from the inhaled air flow must be high enough, but also the type of dispersion force may be of importance [56]. Dispersion forces during inhalation can be increased by increasing the flow rate, but this is at the cost of lung deposition; at a higher flow rate more particles are deposited (and thus lost) in the oropharynx [33]. This perception has led to the 'balance the forces' concept presented in chapter 1. When the dispersion forces can be increased, e.g. by utilising the available kinetic energy of the inhaled air stream more effectively and/or by deriving a different type of dispersion force, controlling the interparticulate forces in the powder becomes less relevant and higher fine particle fractions can be obtained, although there is a limit to what can be achieved. From tests with centrifugal forces it is known that it takes about ten times as much force to remove 98% of particles from a

surface as that required for 50% removal [36]. The choice for the type of dispersion forces to apply may put a strain on the design of the inhaler. Inertial (vibration or impact) forces are proportional to the third power of the particle diameter and, therefore, the highest of all types of dispersion forces [56], but their application implicates particle impact with inhaler parts which can result in particle accumulation against these parts. The severity of accumulation depends basically on the same variables (chemical nature, crystal habit and particle properties) as those relevant to the interparticulate forces. However, interparticulate forces in accumulated drug fractions may be strengthened by tribocharge effects and the high velocity with which particles collide with previously deposited particle layers. This applies stress on these layers which can lead to powder densification by particle re-arrangement and compaction into a more coherent powder coating. For micronised tobramycin, which appears to be a highly compactable material, this leads to extreme powder retention in the Twincer™ (developed for colistimethate sodium) which was the inducement for the development of the Cyclops (chapter 4). This development has brought the awareness that optimisation of inhaler design must not only be sought in balancing between the interparticulate, dispersion and deposition forces, but (when inertial separation forces are used, as in air classifier technology based inhalers) also between dispersion and accumulation forces. This awareness is accompanied with the understanding that the powder properties remain of utmost importance for inhaler development and that powder cohesiveness, adhesiveness and compaction behaviour need to be known for optimising the inhaler design.

Measurement of the cohesion, adhesion and compaction behaviour of particles is common powder technology practice. However, for expensive micronised or spray dried drug particles, which are mostly only available in very small quantities, suitable techniques are scarce. For measurement of the force of particle adhesion to a surface, traditionally only three methods, generating centrifugal, aerodynamic (hydrodynamic), or vibrational forces are used [55]. More recently, atomic force microscopy (AFM) to measure the cohesive force between drug particles and the adhesive force between drug and carrier particles (α -lactose monohydrate) in adhesive mixtures has been added to the list of possibilities [57]. This technique has been elaborated into the so-called cohesion-adhesion balance (CAB) which can be used to rank different drug-drug and drug-carrier combinations. This ranking is then used to predict the *in vitro* deposition performance and dispersion mechanisms of these drug-carrier combinations [58]. A strong limitation of this technique is that the effect of stress (as during mixing or upon particle impact with accumulated particle layers during inhalation) on the adhesive force cannot be taken into account effectively. They also yield

information over very small surface areas which may not be representative for the whole powder. Furthermore, for all techniques mentioned, it is of utmost importance that the effect of RH on the force of adhesion is taken into account.

For the measurement of the cohesiveness of powders traditionally apparatus like jolting volumeters (yielding the Hausner ratio or Carr's index) and (Jenike) shear cells are applied. Also the angle of repose or the powder flow from funnels with decreasing diameters are frequently applied methods. They demand large volumes of powder which are mostly not available in the development stage of dry powder formulations for inhalation. An interesting new approach is the powder strength distribution model [59]. This model on de-agglomeration in cohesive lactose powders describes that parameters like particle size, work of adhesion (a function of surface free energy) and packing fraction (all three variables determining the agglomerate strength) are non-homogenous in a powder and therefore, the powder strength is also heterogeneous. This new approach for calculating powder strength distributions provides new insights into powder de-agglomeration during inhalation. The concept can be further applied in cohesive pure drug formulations for high dosed medicines like antibiotics. Recently, Grasmeijer et al. presented the energy ratio distribution concept which is comparable to the previous concept, but has an application specifically for adhesive mixtures [60]. In contrast to the de-agglomeration of cohesive powders, dispersion of adhesive mixtures primarily concerns the detachment of drug particles from the surface of large carrier crystals. Multiple variables (e.g. drug and carrier particle surface roughness, local carrier surface composition, number of contact points per drug particle, drug particle shape, size and orientation on the carrier surface, and variables of the mixing process) determine the 'potential separation energy' ($E_{s,pot}$), and the 'binding energy' (E_b) is determined by the strength of the drug-carrier interaction. Detachment of a drug particle from the carrier surface occurs when its energy ratio $E_{s,pot} / E_b \geq 1$. Because of the variability of the parameters that determine drug detachment, dispersion behaviour should not be assessed at a single inhalation flow rate as is often the case [60].

Because all techniques for powder characterisation mentioned above are indirect measures for dispersion and retention behaviour in a DPI, we chose for the approach to measure these phenomena in the inhalers used for our studies, being the TwincerTM and the Cyclops. Although for future studies additional methods may be desired for classifying drugs upon their physico-chemical properties relevant to efficient dry powder inhalation, only testing in the dispersion and administration device itself yields the information needed for optimisation of the design of that device.

Summary and conclusions

The physico-chemical properties of a compound largely influence its dispersion efficiency and retention in a given type of DPI. Aminoglycosides, more specifically tobramycin, are a class of drugs notorious for their adverse solid state properties with regard to dry powder inhalation. Recorded moisture isotherms, visual observation and dispersion experiments revealed that aminoglycosides are highly hygroscopic and become wet on their surface by moisture sorption already at a low RH of 30–40%. Because there exists only a minor difference in moisture sorption between the crystalline and amorphous (spray dried) tobramycin base, and because spray dried particles gave better dispersion performance in the Twincer™, we chose to use spray drying as preferred preparation technique. The free base furthermore absorbs considerably less water than the sulphate, particularly above 50% RH (Figure 3.2), and has the advantage of a lower molecular weight, which reduces the dose to be inhaled. Following the formation of surface layers of water, the drug particles start to dissolve, forming a sticky and highly viscous syrup. From this point of moisture sorption, which equals about 8–12% water by weight for the crystalline and spray dried tobramycin base respectively (Figure 3.2), dispersion is impossible and inhaler retention equals almost the entire dose. Water sorption and eventually complete liquefying of particles after exposure to RH-values higher than 60% is the main reason why the powders should be processed in an atmosphere with low RH and aminoglycoside DPIs should be disposable. Moisture sorption of residual powder within the device wets internal inhaler parts and this is fatal for dry powder inhalation. Processing of tobramycin, as with PulmoSphere™ technology for TOBI®, may slow down the moisture sorption rate, but although particles seem to maintain their powdery appearance up to high RH-values, tests showed that drug dissolution (and inhaler wetting) cannot be prevented. Merely the excipient shell remains intact, whereas the drug is leached out.

Also at lower RH-values, aminoglycoside particles tend to adhere onto inhaler parts upon making contact with them and this puts a strain on the design of the inhaler when making use of inertial dispersion forces, as in the classifier based Twincer™. In this inhaler, dispersion relies primarily on particle-particle and particle-wall collisions and an optimisation may be needed in terms of dispersion and retention. This awareness has been the starting point in the next chapter for the re-design of the Twincer™ into the Cyclops as an efficient high dose disposable DPI for dispersion of this excipient-free formulation with limited inhaler retention.

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