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DOSAGE FORMS AND FORMULATIONS FOR DRUG ADMINISTRATION TO THE RESPIRATORY TRACT

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INTRODUCTION

At diseases in the respiratory tract, there is a possibility to reach the target organ directly and to get a local effect of the drug. In other cases, drugs are administered into the respiratory tract in order to obtain a systemic effect after absorption from the upper or the lower airways. Systemic treatment after absorption from the lower respiratory tract is not widely used but there are examples such as ergotamine and insulin which have been administered as inhalation aerosols. Probably, the preconditions are better to administer reproducible doses of a drug into the upper respiratory tract, that is the nose, for systemic effect. In recent years, there has been a large interest in nasal administration of drugs, as it has been shown that some drugs are rapidly and completely absorbed from the nasal mucosa[1]. Drugs of interest are those which are inactivated in the gastrointestinal tract after per oral administration and those with extensive first pass

metabolism, and when a rapid onset of action is needed. Nasal administration may then be an alternative to the parenteral administration. Several peptides are now on the market for nasal administration and other drugs are studied, such as meclizine, naloxone, propanolol and progesterone[2-5]. However, it is important to investigate the new way of administration carefully as there is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the drug substance and from constituentia added to the dosage form. By definition, the oral cavity is also a part of the upper respiratory tract. However, drugs intended for administration to the oral cavity only, will not be covered in this review.

Drugs are widely used for local effect in the lower respiratory tract. Bronchodilators, corticosteroids, anticholinergics and antiallergic drugs are administered as inhalation aerosols, the advantages being decreased systemic side effects and in some cases rapid onset of action. It is supposed that the drug must reach the lower respiratory tract to give the local effect. At oral inhalation, most of an aerosol dose is deposited in the upper airways and a small fraction is exhaled. Thus, only a small fraction of the dose is reaching the lower respiratory tract to give the local effect. For bronchodilators it has been shown that the buccal administration of low doses does not cause bronchodilatation[6-7]. In the case of corticosteroids, the oral deposition may cause side effects[8]. Local administration of nasal decongestants, corticosteroids and antiallergic drugs is also widely used. Because of the accessibility of the nasal mucosa, both inhalation aerosols and other dosage forms can be used.

There are few drugs in gaseous form. Otherwise, this would be an advantageous form for the penetration

into the respiratory tract at inhalation. Instead, many drugs can be formulated into aerosol dosage forms that are administered with the inhaled air. It is important to know the main physical mechanisms according to which aerosol particles are deposited on the surface of the airways: Impaction of particles is depending on the mass and velocity of the particles and it is occurring in the upper respiratory tract and at other changes of direction of the air flow. Particles that have penetrated further into the airways may be subject to a sedimentation onto the mucosa. The degree of sedimentation is depending on the mass of the particles but also on the time a particle is allowed to stay in the airways. Diffusion is the third main mechanism for aerosol deposition but it is only important for very small particles, below 0.5 μm. Diffusion is also time dependent. For aerosol dosage forms used in clinical practice, diffusion is of minor interest. Thus, the deposition of aerosol particles depends on variables of the dosage form, such as aerodynamic size and particle velocity, but also on the breathing pattern of the subject and patho-physiological conditions of the respiratory tract[9–11]. Most of the large aerosol particles impact in the upper respiratory tract, and sedimentation occurs during the residence time of aerosol, before exhalation. Water soluble drugs will grow during the transport in the airways because of the high relative humidity. This results in an earlier deposition in the airways compared to insoluble particles[9,12]. It is evident that the patients can influence the deposition pattern of an aerosol from their inhalation manoeuvres. The fraction into the lungs can be increased from a low air flow at inhalation and a long time of breath-holding[13]. In obstructive lung diseases, the penetration of an aerosol is impaired and the particles are deposited more centrally. This fact seems to be a disadvantage when a local effect is required in the obstructed areas.

After deposition, the drug must exert its local effect or must be absorbed before it is cleared from the respiratory tract. In the nasal cavity, cilia are present in the posterior two thirds. The mucociliary clearance is rapid in the nose, removing foreign particles mainly within 30 minutes. Drugs deposited in the anterior part of the nasal cavity may stay for longer periods if they are not absorbed. In the lower respiratory tract, the mucociliary clearance is completed within 24 hours but there are no cilia in the peripheral airways. In these parts, the clearance is slow and it is mainly occurring from phagocytosis. Such particles may stay for months in the airways[9]. A sudden removal of deposited drug may occur from coughing which reaches the lower respiratory tract to about the 7th generation, or from sneezing.

Some dosage forms are similar for administration into the upper or the lower respiratory tract. Powder aerosols, pressurized aerosols and aqueous dosage forms are all used but there are differences in the formulations and the design of the dosage forms depending on the use in the nose or into the lungs.

POWDER AEROSOLS

Powder aerosols are used both for oral and nasal inhalation. For penetration into the lower airways it is generally accepted that the majority of particles should be smaller than 5 μm. A crystalline drug substance can be precipitated to this size, or micronized in a ball mill or a jet mill. In the micronizing process, the drug substance may be contaminated from the grinding parts or from the compressed air and the collecting filter. Oil droplets should be separated from the compressed air and the moisture content should be low in the case of moisture sensitive drugs.

It is necessary to measure the particle size distribution of the drug substance intended for inhalation. Usually, an ordinary light microscope is used to describe the appearance of the particles and the presence of agglomerates. In order to get reliable results, a large number of particles must be measured and an automated procedure is needed for the routine controls. It is then important to take a representative sample of the powder and to disperse it carefully, otherwise agglomerates may be measured as individual particles. In some cases the Coulter Counter technique can be used to characterize the particle size distribution. This procedure requires that the drug substance is suspended in an electrolyte, but many drug substances used for inhalation are polar. Even a low solubility can interfere with the results as small particles will dissolve and precipitate on the larger particles. The problem is more pronounced at uncontrolled temperatures during the measurements.

An inhalation device is required in order to disperse the drug substance to a powder aerosol. The first successful powder inhaler was Spinhaler, introduced by Fisons Ltd for sodium cromoglycate[14]. Spinhaler containes a rotor, where a gelatin capsule is inserted by the patient. The capsule keeps a single dose of the micronized substance. When air is inhaled through the device, the rotor causes a vibration in the capsule, and the contents are dispersed into the inhaled air. The critical air flow for the vibration is about 35 l/min which is the minimum air flow rate to generate the powder aerosol. It is an advantage that the powder aerosol is only produced at the phase of inhalation but there is no mechanism to prevent an exhalation through the device. This can be a problem as moisture is then introduced into the device and may be sorbed by the drug

substance. The accuracy of filling a single dose of the micronized drug into the gelatin capsule is dependent on the flow characteristics of the powder. The micronized powder has a poor flow which makes it difficult to fill the capsule with an exact dose. One way to improve the flow characteristics is to add coarse lactose particles, mainly 30 to 60 μm. Another problem is then to break up the particle bondings effectively between the fine drug substance and the coarse carrier substance. A turbulent air stream is needed to disperse the fine particles but the efficiency is limited by the ability of the patient to make a heavy inhalation. It is a problem that a high air flow rate is required when a powder inhaler is operated in order to break up the interparticulate bondings and form an acceptable aerosol for inhalation, but a low air flow is required to avoid impaction in the upper airways. There is obviously an optimum between these conflicting requirements. Some patients may also find it difficult to inhale at a high flow rate.

The inhalation of a powder into the respiratory tract may cause irritation and coughing. Various drug substances and carrier substances may be different in this respect, but the concentration of the aerosol particles is also important. As the use of a carrier substance will increase the amount of powder inhaled it is an advantage if the carrier substance can be excluded from the formulation. In a further development, Fisons Ltd succeded to eliminate the coarse carrier substance and the flow of the micronized substance was improved from a controlled aggregation of the substance. However, it is equally important that these aggregates are effectively dispersed as the aerosol is inhaled.

Hard gelatin capsules are used as a unit dose system for Spinhaler and other powder inhalers. It is

convenient as there are commercial filling equipments available for the capsules. When the capsule has been inserted into the inhaler by the patient, it must be opened so that the contents can be emptied. In the case of Spinhaler, it is achieved by needles which pierce the capsule wall. The water content of the gelatin must be controlled to get defined perforations.

Further to Spinhaler, other powder inhalers have been designed based on the use of gelatin capsules as single doses of the drug. ISF in Italy modified the inhaler for sodium cromoglycate capsules in such a way that the capsule is rotating like a propeller at inhalation. The drug substance is then ejected from the openings in the capsule. In Spinmatic, Fisons Ltd has made a similar design to disperse the drug into the air stream. Rotahaler, Glaxo Ltd, was developed for oral inhalation of salbutamol and beclomethasone dipropionate[15]. The gelatin capsule is opened in two halves and the contents are then available for inhalation. The resistance to air flow seems to be lower in Rotahaler compared to Spinhaler and the contents of the capsule are emptied more easily. However, it is necessary that the patient is inhaling with a high air flow rate to disperse the drug substance properly in order to get a good efficacy of the drug[16]. Clinical comparisons have been made between the use of salbutamol in Rotahaler and a pressurized aerosol. It seems as the powder aerosol is equivalent[17] or less potent[18] compared to the pressurized aerosol. Boehringer-Ingelheim has developed a powder inhaler for fenoterol[19] that is available in some countries in addition to the pressurized aerosol. The resistance to air flow is high in this device but it seems to be effective to disperse the drug into the inhaled air. In a clinical trial it was shown that a significant effect was obtained at a very slow inhala-

tion also[20]. In a comparative study on asthmatic children, the bronchodilator effect of the powder inhaler was shown to be equivalent to the pressurized aerosol[21]. The powder aerosol systems described above are all similar and are based on the use of single doses in gelatin capsules. In some products, a carrier substance is needed to get an accurate filling of the dose into the capsule. Such constituents should be minimized or eliminated. Further improvements are likely to be made in the design of the inhalers as they are complicated to use in an acute situation.

A powder inhaler was also developed by Fisons Ltd for nasal inhalation of sodium cromoglycate. The drug substance is insufflated into each nostril from a nasal inhaler. The break up of the drug substance into primary particles is not critical for the nasal administration but the dose should be effectively distributed into the nasal cavity and a large dose of powder should be avoided as it may cause irritation on the nasal mucosa. There are few powder aerosols for nasal inhalation and it is more common to use other dosage forms for nasal administration.

Testing of Powder Aerosols

Pharmacopoeial monographs for powder aerosols will probably be introduced in the near future. However, it is evident that testing should include both the dose of the drug and the particle size distribution. The dose leaving the inhalation device is always lower than the dose in the gelatin capsule. Some losses are due to drug substance remaining on the walls of the capsule and to impaction of the drug inside the inhaler. The dose leaving the inhaler should be determined but it is then important to know the influence of the air flow rate

through the device. The volume of air through the device will also be of importance to the degree of emptying from the capsule.

Particle size is an important parameter determining the penetration of the aerosol into the airways. The micronized drug particles are difficult to deaggregate and it is necessary to know how efficiently this is occurring in the recommended inhaler. It is then important to use a relevant air flow rate through the inhaler compared to the use by the patient. Inertial methods are used[14,22,23], such as a cascade impactor, in which the aerosol cloud is dynamically fractionated. When only the drug substance is used, other sizing instruments can also be utilized as it is not necessary to differentiate between drug particles and particles of the constituents. Laser holography[24] can be used to measure the aerosol particle size directly in the aerosol cloud. In light scattering procedures[25], the aerosol must be diluted before the measurement. This may give false results, as large particles and aggregates are lost before they reach the measuring zone. Methods for aerosol measurements are described more in detail elsewhere[26,27].

Water sorption of the dosage form should be investigated with respect to possible changes in physical and chemical characteristics at various storage conditions during shelf life. It is also interesting to determine water sorption and particle growth at relative humidities similar to those in the airways but it is difficult to obtain relevant in vitro models with such high relative humidities.

PRESSURIZED AEROSOLS

The pressurized aerosol, or metered dose inhaler, is a widely used dosage form for both oral and nasal

inhalation. The drug substance is dissolved, or more frequently suspended in a liquid propellant mixture. The propellants consist of various chlorofluorocarbons identified by a numbering system. The propellants have sligthly different solubility properties and contribute in various respects to the vapour pressure in the aerosol vial. Propellant 11 has a high boiling point and can be handled at room temperature which makes it possible to produce a concentrate with the drug substance using conventional equipment. The other propellants are then added to the final volume and to the required vapour pressure. The use of chlorofluorocarbons has been questioned with respect to toxicity and possible destruction of the ozone layer in the atmosphere. However, the pressurized aerosols are now regarded to be safe to use according to the instructions to patients. There are restrictions in the use of chlorofluorocarbons in some countries but the use in medicinal aerosols has been extempted. The propellants are non-polar liquids in which most drugs have a low solubility. This is an advantage for the physical stability when a suspension is formulated. The solubility can also be influenced from the choice of salt of the drug substance or from the propellant mixture. In some cases, the drug may form modifications of the crystalline structure with a propellant but the physical stability can then be improved by a pretreatment of the drug substance with the propellant[28]. When a suspension of micronized drug is formulated, the particles have a very high surface energy and tend to form aggregates. A surfactant is then added to the composition to make the suspension homogeneous. Low concentrations of sorbitan trioleate, oleic acid or lecithin are used in inhalation aerosols. These surfactants are non-volatile liquids which are dissolved in the propellants and they will appear in the generated aerosol together with the drug particles[29]. A solution

of the drug substance in the propellant mixture may also be obtained, but often large amounts of ethanol or another co-solvent is needed to get a proper solution. Such an additive can be irritating to the mucosa and will also influence the particle size of the generated aerosol as the co-solvent is less volatile than the propellants. A solution aerosol is physically more stable than a suspension but the chemical stability is often inferior.

The filling of the pressurized aerosol can be made by a pressure filling technique or by a cold filling technique. When pressure filling is used, the design of the metering valve sealing the vial must allow the contents to be forced through it. When the pressurized aerosol is actuated by the patient, a dose of liquid is dispensed from the vial by means of the metering valve. The volume of the dose can be changed between 25 to 100 μl dependent on the design of the valve. The materials in the valve may vary. When plastic is used, attention must be paid to the risk of drug sorption and swelling of the plastic. Rubber gaskets are used in the valve in order to get a satisfactory seal. The rubber gaskets may also absorb drug substance. It is advantageous to store the aerosol vial upside-down to prevent the rubber gaskets to dry. Some of the contents will always remain in the vial which cannot be completely emptied through the valve. For this reason, additional liquid must be filled into the vial to ensure that the labelled number of doses can be actuated by the patient. Some of the propellants is also allowed to leak out of the package during storage and this leakage is compensated for at the filling stage.

When a dose is actuated from the pressurized aerosol, a metered volume of the contents is released

through the valve stem to the actuator. As the liquid propellants meet the atmospheric pressure, some of the propellants is evaporating suddenly[30] and the remaining liquid is fragmented into irregular fractions. The change is very rapid and the heat required for the change from liquid phase to gas is taken from the liquid propellants which are chilled down. The liquid fragments are then forced through the actuator orifice towards the patient. Further evaporation of the propellants is occuring as the droplets are passing through the air. This is a slower evaporation compared to the initial phase. Thus, the size of the droplets containing the drug substance depends on the distance from the actuator orifice or the time for propellant evaporation. The use of a co-solvent to the formulation will reduce the evaporation rate of the liquid further and results in larger aerosol particles[31,32]. With respect to the possible impaction of aerosol particles, it is not only the size of the particles that is of interest but also the velocity. It seems as the aerosol droplets which are ejected from the actuator orifice have a very high initial velocity, but the particles are decelerated by air resistance[33]. The combination of large particles and high velocity close to the actuator orifice favours the impaction of the aerosol particles at a short distance. An increase in the vapour pressure produces smaller particles[34] but increases the initial velocity of the particles. Indirect measurements were performed in order to investigate the deposition pattern of terbutaline after oral inhalation from pressurized aerosols with various vapour pressures[35]. An increased vapour pressure seemed to improve the availability of the drug to the airways. These results were supported by a study with Teflon particles labelled with a radioisotope of technetium[36]. A change in the metering volume of the valve may also influence the deposition pattern, as an addi-

tional amount of liquid propellants is released to be evaporated. For oral inhalation, it appears that the metering volume should be small in order to improve the availability of the drug to the airways[35,36].

The actuator of a pressurized aerosol is important to generate the aerosol particles and to direct the dose to the patient. A small orifice will produce small particles, but clogging may occur if the orifice is too narrow, especially when a suspension is actuated. For oral inhalation, the actuator can also be essential to decelerate the aerosol particles and to allow evaporation of the propellants before the aerosol will reach the subject. Extension tubes and inhalation chambers can be attached to the conventional actuator in order to increase the distance to the patient. Thus, the impaction of aerosol particles can be reduced in the upper airways and a larger fraction of the dose may reach the lower respiratory tract. Indirect measurements were performed to investigate the deposition pattern after inhalation of terbutaline through various extension tubes[37]. The deposition was reduced significantly in the mouth, and probably the availability of the drug was increased to the remaining parts of the airways. The same actuator and tubes were also tested in a deposition study using insoluble Teflon particles labelled with technetium[38]. The deposition in the upper airways decreased and the deposition on the conducting airways increased significantly as the extension tubes were added to the actuator. A small extension tube was utilized on a pressurized inhalation aerosol containing triamcinolon acetonide[39]. It was effective for reducing drug deposition in the oral cavity. This could be beneficial especially for inhalation of steroids to decrease local side-effects such as hoarseness or thrush due to high local concentrations of the drug in the upper

respiratory tract[40]. Valves can be added to the extension in order to control the air flow for inhalation and exhalation, allowing the aerosol to be carried only by the inhaled air to the patient. Correlation of the actuation and the inhalation is then unimportant which makes it possible for a larger group of patients to be treated with a pressurized aerosol. Various designs of breath controlled tubes and inhalation chambers have been described for oral inhalation[41-49].

Pressurized aerosols are also used for nasal inhalation. It is interesting that the same formulations of pressurized aerosols are used for nasal inhalation with the aim to get a high deposition in the nasal cavity and a low penetration into the lower airways, as for oral inhalation with the aim to get a high deposition in the lower airways and a minimum deposition in the upper airways. However, a high impaction can be expected at nasal inhalation because of the short distance from the inhaler and the nose. The anatomy of the nose will also favour a high impaction of aerosol particles and a low penetration into the lower airways. The risk of a high local concentration of drug at the location of impaction has been pointed out[50] and it was suggested that the dose from the pressurized aerosol is actuated in two separate directions in order to increase the aerea of deposition in the nasal cavity. In an in vitro model, it was shown that the impaction is high when the pressurized aerosol is actuated into the nose, and the nasal otium seems to be a hindrance for the penetration of the aerosol into the nasal cavity[51]. In a radioactive deposition study using Teflon particles labelled with technetium[52], it was shown that most of the dose from a pressurized nasal aerosol is impacted in the anterior part of the nose and about 20 % is eliminated by means of mucociliary clearance, indicating that

this fraction had penetrated to the ciliated region of the nasal cavity. No detectable amounts were found in the lower airways. It was also shown that the change of direction of actuation did not improve the deposition pattern significantly. At inhalation, there is a risk of irritation of the nasal mucosa when a large volume of propellants is actuated into the nose[53]. For this reason, it is probably an advantage to use a valve with a low metering volume.

Testing of Pressurized Aerosols

Pharmacopoeial monographs for pressurized aerosols are mainly intended for products for oral inhalation but most of the tests are also applicable to nasal inhalation. Monographs are present in the British Pharmaceutical Codex (BPC)[54] and in the United States Pharmacopoeia XXI-National Formulary XVI (USP-NF)[55]. In both of these, there is a microscopic evaluation of the drug particle size in the case of a suspension aerosol. The majority of particles must be less than 5 μm which is generally accepted for penetration into the lower respiratory tract at oral inhalation. In this test, no attention is given to the real size of the aerosol particles which are generated from the actuator orifice and inhaled by the patient. These particles are always larger than the drug particles as they will contain some liquid propellants and surfactant, and even aggregates of the drug. The continuous change in aerosol size, caused by evaporation of the propellants, can be measured directly in the emitted aerosol cloud by means of laser holography[24,29]. In this method, there is no differentiation between particles containing the drug substance and particles formed from the constituents only. This limitation is also valid for light scattering methods[25]. The sample from a pressurized aerosol cannot

be actuated directly into the measuring zone of a light scattering sizer but must first be diluted. This means that the initial particle size of the aeorosol is changed before the measurement is performed and large particles may be lost during the transport. These limitations also apply to the interpretation of the results obtained from the single-particle aerodynamic relaxation time analyzer[56]. Evidently, particle size is one parameter that is of interest in order to predict the deposition and penetration of the aerosol in the respiratory tract. But particle velocity should also be characterized directly or indirectly as it is another parameter determining the deposition of the aerosol. The inertial separation methods can be designed to measure the impaction likely to occur in the upper respiratory tract. A bent glass tube is then used to simulate the throat before the first stage of the impactor[23,24]. Other in vitro models have been used to simulate the appearance of the respiratory tract at oral inhalation[32,39] or at nasal inhalation[51]. An inertial separation model seems to be more suitable to use for particle characterization in a pressurized aerosol than the microscopic evalution of the drug substance that is now performed in BPC and USP-NF. However, it is important to point out that some time will elapse before the aerosol particles are impacted on the various stages of the sizer and this means that the particles have changed in size and velocity compared to the particles generated from the actuator orifice. When the aerosol particles have been inhaled, they may grow in size because of water sorption. It is difficult to predict the growth rate of drug particles in a pressurized aerosol, as it may be delayed from the presence of the propellants and the surfactant. From the examination of the exhaled particles, it is possible to find out if water sorption has occured[57].

The pressurized aerosol is a multiple dose system and it is necessary to characterize the dose from it. The volume of the metered dose can be determined to evaluate the valve function, and in a solution aerosol it can also be used to characterize the dose of the drug. In a suspension aerosol, the dose will be more variable. The dose available to the patient is determined both in BPC and in USP-NF, but the procedures for sampling are different. The dose available to the patient is not a measure of the availability at the intended site of action in the respiratory tract. The bioavailability is dependent on such variables as the formulation of the pressurized aerosol and the physicochemical characteristics and the aerodynamic size of the aerosol particles. It is also influenced from the breathing pattern, and any pathological conditions in the respiratory tract. No such in vitro model is available, but the tests required in BPC and USP-NF should be performed in a way that reflects the use of the pressurized aerosol by the patient. The in vitro dose sampling should be performed on the basis of actuation into air and not into liquid as in the BPC test[58], and a fixed interval between actuations should be specified. In the case of oral inhalation, the air flow rate should be increased as compared to USP-NF[58]. A proposal for specifications and methodology for dose delivery has also been presented by Scharmach[59].

An assay of the contents in the pressurized aerosol is performed in order to check the variation in the manufacturing process. The recovery in the sampling procedures in BPC and USP-NF has been investigated[60]. Actuation under the surface of chloroform resulted in a low recovery, as a fraction was probably lost into the air. It seems to be a better alternative to chill the contents, open the vial cautiously, and determine the drug after evaporation of the propellants.

The high vapour pressure in the vial requires that the seal is efficient to prevent losses of the propellants during storage. A weight loss test is specified for leak testing according to USP-NF. The test is performed after manufacturing, and the aerosol vials are stored for a short period and the weight loss for one year is extrapolated from the results. As weight loss is usually decreasing during storage of the filled units, such an extrapolation does not give a true figure of the annual weight loss.

The plastic moulding of the actuator orifice is crucial, as the orifice is involved in the generation of the aerosol particles. It is also determining the direction and velocity of the aerosol particles. The moulding of the actuator can be checked from the drug retention in the actuator after firing doses through it into the air[58]. A technique has been described to characterize the pattern of the aerosol cloud by means of video images[61].

AQUEOUS DOSAGE FORMS

Water can be used as a vehicle for the administration of a drug in a solution or a suspension into the respiratory tract. For inhalation into the lower respiratory tract, the liquid must be fragmented into small particles by means of a jet nebulizer or an ultrasonic nebulizer. An oral inhalation is more efficient for the penetration of an aerosol to the lower airways compared to a nasal inhalation[62]. When the target organ is the nasal cavity, a less complicated administration can be used. A hand-operated pump spray is efficient enough to form an aerosol which can be administered into the nasal cavity and the administration of nose drops is also an alternative.

The formulation of the drug in a solution is often preferred, as a suspension is likely to cause problems with the physical stability and requires some precautions to get reproducible doses to the patient. In some cases, the solubility of the drug is pH-dependent and the pH must be adjusted in order to get the right concentration. It may also be necessary to add a co-solvent such as ethanol, polyethylene glycol or propylene glycol. In the case of an inhalation aerosol, the co-solvent may change the aerosol characteristics, as it changes the surface tension and the viscosity of the liquid. Co-solvents which are more volatile than water, will increase the evaporation rate of the liquid in the aerosol droplets. The possible irritation caused by the co-solvent should also be considered, and it may cause a burning sensation and coughing. A solubilization can also be practised to dissolve the drug substance. Then, a surfactant is added in a concentration above its critical micelle concentration and micelles are formed in which a non-polar drug can be dissolved. The availability of the drug from the micelles must be investigated carefully. Sometimes, there are reasons to formulate a suspension of the drug. Then, the physical stability must be investigated, as well as the possiblity to redisperse the suspension at use. When the product is filled into a multidose container, it is necessary to study the accuracy of the dose. The addition of a surfactant and thickening agent is often needed to make a satisfactory suspension. These additives may influence the possibility to fragment the liquid into small drops.

The selection of the final pH for the liquid may depend on the solubility of the drug substance, but also on the stability of it. Many drugs are more stable at an acidic pH, and the adjustment of the pH should then be performed with a strong acid, as it results in a low

buffering capacity of the liquid. The pH will then change readily as the liquid is reaching the mucosa in the respiratory tract. Liquids administered into the respiratory tract should be isotonic in order to avoid an irritation[10]. In the case of an inhaled aerosol, the isotonic droplets will stay relatively unchanged at the high relative humidity in the airways but hypotonic and hypertonic liquids will shrink or grow rapidly. The possible oxidation of a drug substance can be prevented by the addition of an inert gas such as nitrogen or carbon dioxide in the finished dosage form. The gas protection is only effective as long as the package is sealed. An oxidation is often catalyzed from the presence of small amounts of heavy metals which can be reduced by the addition of complexing agents such as EDTA and citric acid. Bisulphites should be avoided as they are irritating to the airways and they may even cause allergic reactions[63]. In a multidose package, the formulation must contain a preservative agent. Preservatives such as chlorobutanol, parabens and benzalkonium chloride are added in dosage forms intended for the airways. Some preservatives are suspected to exert a damage on the cilia activity[64], and preservatives have also been reported to cause allergic reactions[65]. If possible, preservatives should be avoided in formulations intended to be administered to the respiratory tract.

The liquid intended for use in a nebulizer is filled in unit doses or in a multidose package. Preferably, the drug should be filled in unit doses which are ready for administration. Furthermore, preservatives and other stabilizing agents may be avoided in the unit dose package. Double ended glass ampoules are filled as a unit dose system as well as plastic units. As the plastic material is permeable, oxygen may diffuse into

the liquid and cause an oxidation while the solvent may evaporate from the package. The potential stability problems can be reduced by use of a tight foil around the plastic container. Preformed plastic units can be filled with the nebulizing liquid, but the bottle-pack technique is more elegant as the unit doses are formed, filled and sealed in sequential steps in one machine to form a sterile product without preservatives.

The jet nebulizer requires compressed air to operate. The compressed air enters the nebulizer through a capillary close to a liquid feeding capillary. The liquid is broken up to form droplets of various sizes and the large particles are sorted out of the primary aerosol from impaction by means of baffles. The impacted droplets return to the bulk liquid and the aerosol is leaving the nebulizer to be inhaled. The large volume of air passing through the nebulizer takes up water, and the liquid is cooled down. The loss of water causes a continuous increase in the drug concentration in the nebulizer[66,67], and the concentrating effect is high at the end of the inhalation. The output of aerosol droplets from a jet nebulizer differs among the various designs, and there is a reduction in droplet size with increasing compressed air flow rate[67–70] and simultaneously a reduction in nebulisation time[71]. Furthermore, aerosol release is more efficient when the volume fill is increased. The formulation of the liquid may also influence the fragmentation into droplets, from such variables as the surface tension[67] and the viscosity[72].

Ultrasonic nebulizers use high-frequency sound waves from a piezoelectric crystal in order to cause the fragmentation of the liquid into droplets. Some of the energy is also converted to heat. Thus, the liquid will aquire a higher temperature compared to room tempera-

ture, in contrast to the liquid in a jet nebulizer. A concentrating effect will also occur in the liquid when the ultrasonic nebulizer is operated[66]. The design of the nebulizer and the characteristics of the liquid will influence the output and the particle size in a similar manner as with a jet nebulizer. However, the rate at which the aerosol is generated is not related to the air flow through the nebulizer.

The flow and penetration of an aerosol into the lungs is dependent on a pressure differential resulting from the patient's inspiratory effort. The use of a positive pressure may increase the pressure differential. One method of increasing the pressure differential is by means of intermittent positive pressure breathing, IPPB, which increases the pressure differential during inspiration. However, is has been shown that IPPB gives less penetration, less peripheral deposition and a lower total lung dose of radioactively labelled particles compared to spontaneous breathing[73], and its use is debatable.

When the same drug substance is used in a nebulizer and in a pressurized aerosol, the recommended dose for the nebulizer is always much higher. The reason could be that more severely ill patients are treated with a nebulizer, but it could also be that some patients are over-dosed. In a dose response study with salbutamol, it was found that the dose in a jet nebulizer could be decreased while maintaining the same efficacy in mild asthmatics[74]. The percent of the nebulized liquid that reaches the lungs varies in different studies[74-78], and it is not easy to compare the results from the various studies as different types of nebulizers were used, the formulation of the liquid varied, and the modes of inhalation were different. It is evident that the frac-

tion of the dose reaching the lungs will be different when the aerosol is administered through a face mask, through a mouth piece or from a settling chamber. In a clinical study, it was found that the efficacy in the small airways was improved in asthmatics from the inhalation of terbutaline in a nebulizer producing smaller particles compared to two other types of nebulizers[79]. Thus, the choice of nebulizer could be important for the results of the treatment. Very often it is claimed that the patients benefit from the inhalation of water in the dosage form. However, it should be pointed out that the quantities of water delivered from these dosage forms to the lungs is very low and it has not been clearly shown that the liquid is of clinical benefit. Many patients who are now using a nebulizer can change over to a pressurized aerosol, possibly combined with an extension chamber, and get an equivalent effect of the drug[80].

For nasal administration of the drug, the nose drops can be filled in a multidose container provided with a nasal pipette, or preferably from a hygienic point of view, into unit dose containers filled with the bottle-pack technique. This package will again be advantageous to avoid preservatives and other stabilizers in the nose. Many subjects also find it convenient to use a nasal pump spray which is a multidose container provided with a metering pump mechanism and a nasal actuator. It is important to investigate the compatibility of the formulation with the components of the pump mechanism. The rubber gaskets used to seal the valve may absorbe the drug and the preservative agent, and the plastic components may change during storage.

The nasal pump spray can be designed to meter a dose volume of 50 to 150 μl. A lower volume will give an unacceptable accuracy of the dose, and a higher volume is not suitable as a portion of the liquid is likely to

run out of the nose after administration. In the multi-dose container, the liquid passes through a capillary tube to the metering chamber. A spray is formed as the liquid is forced through a fine orifice in the actuator. The volume of liquid that is dispensed from the container is replaced by air. This replacement is occuring through the valve and not through the actuator which is an advantage as there is no contamination of nasal secretion into the container. The viscosity and the surface tension of the liquid will influence the spray formation and the spray cone angle from the actuator. A low viscosity and a low surface tension will generate smaller particles and will give a wider spray angle. The design of the actuator orifice is also important for the formation of the particles and the spray cone angle. A precompression of the metering valve will assure a uniform pressure when the dose is released through the actuator. All types of pump sprays are not working according to this principle and the properties of the spray could then be variable depending on the force of actuation. Before the first administration to the patient, several actuations are needed before the metering chamber is filled and an acceptable dose can be dispensed through the nasal actuator. Such a priming is also necessary when the container has not been used for some time[81].

The intranasal distribution of nose drops and from a nasal pump spray have been investigated by means of a labelling of the dosage form with technetium[82]. In this study, the administration of three drops gave a better distribution compared with one drop, and the nose drops were better distributed compared with a nasal pump spray. Healthy subjects were studied, but it is evident that diseases in the nose may influence the initial distribution and the clearance of a drug[83]. The radio-

active deposition studies indicate that there are some differences between the nasal dosage forms, but the clinical importance of such differences should be investigated. In clinical trials comparing beclomethasone in a nasal spray and a nasal pressurized aerosol, these dosage forms were found to be equally effective[84,85].

Testing of Aqueous Dosage Forms

The particle size is of particular importance for an aerosol intended for penetration into the lower respiratory tract. The particle size distribution from an aerosol generated from an aqueous system is not easy to characterize, as the droplets change in size due to evaporation. The size of water droplets change rapidly from the point of generation to the point of inhaling them, but the situation is different when a drug or a salt is dissolved in water[86]. The particle size distribution can be measured by the methods described for other aerosol dosage forms, e.g. light scattering, laser technique or inertial separation methods. The cascade impactor has been used frequently in characterizing jet and ultrasonic nebulizers[87,88]. The aerosol from the nebulizer was mixed with dry air and the mixture was collected in a chamber before sampling in the impactor. In this arrangement, the evaporation of the liquid was allowed to occur to a state of equilibrium before the measurement. The original size distribution at the time of aerosol generation could then be calculated. The laser technique has the advantage to allow a measurement of the particle size distribution at a certain distance from the aerosol generation[89]. A change in particle size distribution is to be expected following inhalation of the aerosol into the airways, and the change in particle size can be calculated[66]. For very small particles, less than 0.1 μm, the time it takes to reach the equilibrium

is short compared to the respiratory cycle but long in the case of large particles, larger than 10 μm. Of course, it would be desirable to study the rate of change of an aerosol in vitro but it is difficult to get reliable results as it is difficult to obtain stable conditions of such high relative humidities as in the respiratory tract.

In the case of a nebulizer, the amount of liquid filled into it is always higher than the amount leaving it to the patient. When the nebulizer is no longer generating an aerosol, there is always a certain amount of liquid in the chamber of the nebulizer and in the tubing. The concentrating effect will also cause the liquid remaining in the nebulizer to be more concentrated than the original liquid. This portion will not reach the patient. It is obvious that different doses may be delivered to the target organ when various nebulizers are used. The particle size distribution of the primarily generated aerosol, the baffling system, the concentrating effect, the aerosol output, and the losses in the administration set will all influence the dose to the target organ. The manufacturer of the nebulizing liquid should inform which nebulizers are recommended for use with its product. The dose from nose drops in a multidose container or a unit dose container should be characterized as doses are taken out in a similar way as it is recommended to the patient. The dose from a nasal pump spray is characterized as doses are actuated from it[81,90]. When a homogeneous solution is dispensed, it is sufficient to determine the dose as the weight. In the case of pump sprays, the number of doses needed to prime the pump mechanism should also be determined.

The microbiological condition of the liquid should be investigated when it is inteded to be introduced into

the airways, especially into the lower respiratory tract. Infections could spread easily from a nebulizer which is used by several patients. A microbiological contamination may originate from the device, and efforts should be made to reduce this risk[91]. A low number of viable microorganisms in the liquid product should be specified. When a preservative agent is added to the formulation, the efficacy of the preservative agent should be checked in the finished dosage form. The nebulizer should be cleaned frequently and air-dried or possibly disposed after use.

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