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Review Article

PRESSURIZED AEROSOLS FOR ORAL INHALATION

FOLKE MORÉN

*AB Draco *, Research and Development Laboratories, Box 1707, S-221 01 Lund (Sweden)*

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INTRODUCTION

Pressurized aerosols for oral inhalation are used for drug delivery into the lower respiratory tract, mostly to obtain a local activity in the cases of chronic obstructive lung diseases. Bronchodilators, corticosteroids, and anticholinergic drugs are administered by inhalation, the possible advantages being a rapid onset of action and a low degree of systemic side-effects from a low dose as compared with oral administration for systemic treatment. The site of action after oral inhalation is not well established, but it can be assumed that the drug substance must be able to reach the lower respiratory tract to exert the local activity. At inhalation, not all of the aerosol cloud will be deposited in the lower respiratory tract; the dose is partly deposited in the upper respiratory tract and is partly exhaled. The drug deposited in the oral cavity does not seem to be beneficial for the activity in the lungs. It has been shown that buccal administration of metered doses of a bronchodilator does not cause bronchodilatation (Ruffin et al., 1978). Local side-effects might even occur in the oral cavity after deposition of steroids (Clark et al., 1975).

A great part of the dose available to the patient is swallowed into the gastrointestinal tract, after deposition in the oral cavity and the throat, as well as after mucociliary clearance (Gorman and Hall, 1973). Particles deposited on the mucous blanket are transported by the ciliar movement to the pharynx, where they are eventually swallowed. Mucociliary clearance occurs in all of the lower respiratory tract except the terminal structures. The transport is impaired by various diseases. After deposition in the lower respiratory tract the drug particles must be dissolved in order to exert the local activity; otherwise the drug is removed by the mucociliary clearance.

The deposition of aerosol particles is dependent on such variables as particle velocity, aerodynamic diameter and potential changes thereof, but also on the breathing pattern and pathological conditions in the respiratory tract (Task Group on Lung Dynamics, 1966; Gormal and Hall, 1973; Brain and Valberg, 1979). From studies on dust aerosols, it is known that 3 physical mechanisms are of prime importance to the aerosol deposition: impaction, sedimentation and diffusion. Impaction is dependent on the inertia of particles with a large mass and a high velocity. The large particles are mainly impacted in the

* Subsidiary to AB Astra, Sweden.

upper respiratory tract, and the impaction grows more efficient as the velocity of the particles increases, for instance by the inspiratory air flow. Large particles are also deposited from sedimentation, as the particles are influenced by gravity. Small particles are deposited from diffusion, as these particles are influenced by gas molecules and move at random. The deposition from the 3 mechanisms results in a minimum for particles of about 0.5 μm aerodynamic diameter. Where larger particles are concerned, impaction and sedimentation are predominant, but in the case of smaller particles diffusion plays the main part. Both sedimentation and diffusion are time-dependent, which means that the deposition keeps increasing the longer the particles stay in the respiratory tract. The size for water-soluble particles could change during the passage of an aerosol in the respiratory tract owing to the increased temperature and the high relative humidity. This could result in an increasing diameter and an earlier deposition of the particles (Task Group on Lung Dynamics, 1966; Byron et al., 1977). The change in deposition resulting from different breathing patterns can partly be controlled by the patient. A maximum local deposition of an aerosol in the lower respiratory tract was shown to be obtained from a deep and slow inhalation followed by a breath-holding pause before the exhalation (Pavia et al., 1977). The distribution of the aerosol in the lower respiratory tract is impaired when disease occurs, such as with the obstructive lung diseases asthma and chronic bronchitis. The drug substance might even be prevented from reaching those areas which need to be treated.

GENERATION OF THE AEROSOL PARTICLES

The technology of pressurized aerosols has been covered in textbooks, for instance by Sciarra and Stoller (1974) and by Sanders (1979). In the case of an inhalation aerosol, the drug substance is either dissolved or suspended in the liquid propellants. The propellants consist of chlorofluorocarbons with different boiling points. A mixture of chlorofluorocarbons is often used to obtain the desired vapour pressure. On several occasions, questions have been raised about the human toxicity of the chlorofluorocarbons. Pressurized aerosols are considered to be safe, however, if used in the recommended manner (Lancet, 1975). The use of chlorofluorocarbons has also been criticized for possible destruction of the ozone layer in the atmosphere (Molina and Rowland, 1974). This has led to restrictions in the use of chlorofluorocarbons in some countries. The quantities of propellants used for pressurized inhalation aerosols are small, however, and it even seems to be difficult to find satisfactory alternatives. For these reasons, chlorofluorocarbons have been exempted from restrictions when used for inhalation aerosols. In solution aerosols, large amounts of co-solvents are often needed in order to make the drug substance dissolve in the non-polar propellants. These additives are less volatile than the propellants. Co-solvents can be avoided in suspension aerosols. Suspension aerosols are physically more unstable, however, and therefore non-volatile surfactants are added in small concentrations in order to improve the stability.

The container of a pressurized aerosol is sealed by means of a metering valve which is fitted into an actuator. (Figs. 1 and 2). When a dose is actuated, a metered volume of the contents is released through the actuator orifice. Only a proportion of the propellants flashes immediately into vapour, as the propellants leave the orifice (Wiener, 1958). The flashing is so rapid that the heat required for the change of phase from liquid to gas is

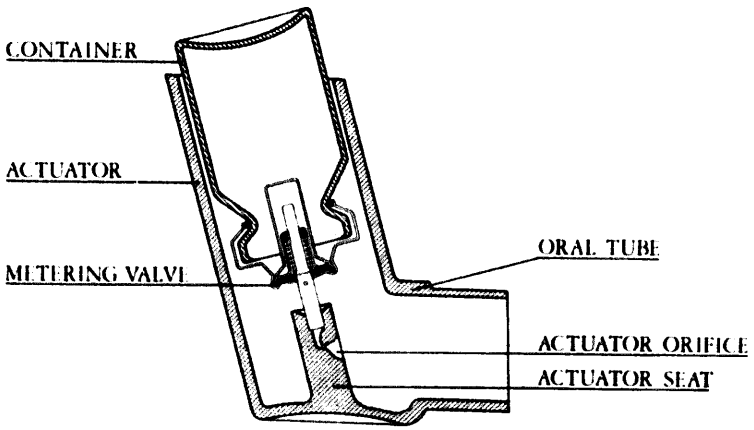

Fig. 1. Pressurized inhalation aerosol.

taken from the propellants. Thus, the remaining liquid propellants are cooled down. Further evaporation occurs during the passage through the air, as energy is acquired from the surrounding atmosphere; the rate of evaporation is low compared with the initial flashing. The size of the droplets containing the drug substance thus depends on the length of time in which the propellants can evaporate, or on the distance from the actuator orifice. The addition of a co-solvent in the formulation will delay the evaporation and generates larger particles (Kirk, 1972; Bell et al., 1973). An increase in the vapour pressure of the formulation, due to a change in the propellant mixture or an increase in temperature, produces smaller particles (Polli et al., 1969). The same effect is obtained by a decrease in the diameter of the actuator orifice. However, clogging may occur if the orifice is too small. This could be a problem with suspension aerosols particularly. The aerosol drop-

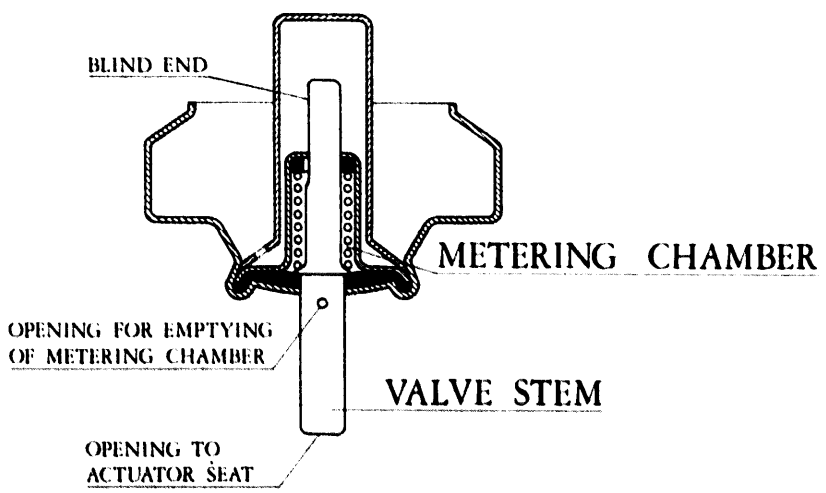

Fig. 2. Metering valve. Reproduced from Morén and Jacobsson (1979).

lets that are expelled from the actuator orifice have a very high initial velocity, but the particles are decelerated by air resistance (Rance. 1974). The resulting aerosol cloud can be seen to have a conical shape.

IN VITRO CHARACTERIZATION

Dose sampling

The dose available to the patient is determined both in the British Pharmaceutical Codex (BPC; 1979) and the United States Pharmacopoeia XX–National Formularly XV (USP XX–NF XV; 1980). It is also required that the dose available to the patient be used for the labelling of inhalation aerosols. The procedures for sampling are different, however. In BPC, the dose available to the patient is determined by subtracting the amount retained in the actuator from the amount delivered by the valve. For the purposes of determining the amount delivered by the valve, the assembled unit is immersed into a reception liquid, and a number of doses are released. The drug substance retained in the actuator is determined after actuation into the free air. In USP XX–NF XV, a unit spray sampling apparatus is used to obtain a sample from the assembled container and actuator. The sampling apparatus consists of an intake tube, a delivery tube to which a sintered glass dispersion bubbler is attached, and a collection chamber containing an absorbing solution. To avoid loss of drug substance into the atmosphere, air is continuously drawn through the apparatus at a rate of 12 ± 1 litres min^{-1}. In the desired procedures, 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 nature and aerodynamic diameter of the aerosol particles; however, it is also influenced by the breathing pattern, the patient's particle clearance, and by any pathological conditions in the respiratory tract. No satisfactory in vitro model is available to cover these parameters. As long as such a model does not exist, the required tests in BPC and USP XX–NF XV concerning the dose delivered to the patient should be performed in a way that reflects the use of the pressurized aerosol in vivo. As drug substance was shown to be retained in the valve stem after the release of a dose into the air, the in vitro dose sampling should be performed on the basis of actuation into the air and not into a liquid as in the BPC test (Morén and Jacobsson, 1979). Furthermore, a fixed interval between actuations should be stated in the methods. In the study, it was also recommended that the air flow-rate be increased as compared with the USP XX–NF XV monographs.

Particle size

In both BPC and USP XX–NF XV, complementary controls are performed on the particle size from suspension aerosols. The determination is made by a microscopic evaluation of a slide onto which the aerosol has been actuated from a certain distance. The size of the crystalline particles is determined. It is required that the majority of particles be below 5 μm diameter, as it is believed that larger particles cannot penetrate into the pulmonary region. In the test, no attention is given to the change in droplet size obtained from continuous propellant evaporation after the generation of the aerosol droplets in the actuator orifice. Neither is the velocity of the particles considered, as they reach the

patient. Both these factors are important for the impaction of the aerosol particles in the respiratory tract.

Other methods have also been described for particle characterization. The change in droplet size can be measured directly in the emitted aerosol cloud by means of high-speed flash photomicrography or laser holography (Hathaway, 1973). In light-scattering procedures, the particle size is indirectly determined in the aerosol cloud (Kanig, 1963), but no differentiation is made between particles containing drug substance or particles from other origins such as the propellants or a surfactant. The sample from a pressurized aerosol cannot be actuated into the measuring cell, but must first be diluted. This means that the initial droplet size is essentially changed during the transport in air before the measurement. The same caution should be made in respect to the interpretation of the results obtained from the single-particle, aerodynamic relaxation time analyzer described by Hiller et al. (1978).

Inertial separation methods have been used to measure the particle size distribution in aerosol clouds (Bell et al., 1973; Hallworth, 1976). By means of a chemical assay, it is possible to determine the drug substance at various stages of the impactor. The recipient volume before the entrance of the impactor should be small, otherwise droplet size and velocity are allowed to change in advance. Other impacting models have been used that are intended to simulate the appearance of the respiratory tract (Kirk, 1972; Sciarra and Cutie, 1978).

Sampling for assay

An assay of the contents in the pressurized aerosol is performed as a control of the manufacturing procedure. National Formulary XIV (NF XIV; 1975) describes an apparatus for sampling the contents of aerosol containers provided with metering valves. The sampling apparatus consists of a pressure tube containing a reception liquid and fitted with a firing adaptor. The container sampling apparatus has been deleted in the USP XX–NF XV. The individual aerosol monographs specify another procedure in which the dose is actuated under the surface of chloroform in a beaker. This sampling procedure for the assay is the same as the one described above regarding the determination of the amount delivered by the valve in BPC. The recovery in the sampling procedures was investigated by Morén and Jacobsson (1980). The procedure involving actuation into a pressure tube was found to be incomplete mainly because of drug retention in the valve stem. The results indicated that a correction should be made for the valve-stem retention. Actuation under the surface of chloroform resulted in a low recovery, as some drug substance was probably lost into the air.

The concentration in the pressurized aerosol container can also be determined from the total amount of drug substance. In this procedure, the contents are chilled below the boiling point of the propellants and the container is cautiously opened. The propellants are allowed to evaporate and the amount of drug substance is then determined.

Actuator

The moulding of the actuator orifice is crucial, as the orifice is important for the breaking down of the liquid into droplets and for the velocity and the direction of the emitted aerosol particles. Miszuk et al. (1980) described a technique with which to char-

acterize the pattern of the aerosol cloud. Two orthogonal video images were utilized to describe the shape and the direction. The technique was used in order to evaluate the quality of the actuator orifice of various samples.

When a patient is breathing through the aerosol actuator, the narrow air passages in the inhalation device cause a resistance to the air flow. As many patients are suffering from obstructive lung diseases, unnecessary resistance to the air flow should be avoided in the device. The resistance can be measured as a pressure drop that increases with higher flow rates. The influence on pressure drop of various inhalation-device designs was studied by Görtz and Morén (1979). The pressure drop was reduced by increasing the area for air passage either in the space between container and actuator, or by using openings in the actuator wall. The aera for air passage was the main determining factor as far as the reduction of the pressure drop was concerned, but there were some differences among the positions tested. The pressure drop across a new actuator design could be accurately predicted by using a friction-loss factor obtained from available results pertaining to an original actuator.

IN VIVO STUDIES

Deposition pattern

The penetration of an aerosol into the human lung can be studied from the scanning of subjects after the inhalation of radioactive tracer particles. For studies of pressurized suspension aerosols, it is necessary to tag the drug substance itself or to produce suitable carrier particles containing a gamma-emitting isotope. Newman et al. (in press, a) used $^{99}Tc^{m}$ incorporated in Teflon particles that were suspended in a propellant mixture before being administered to asthmatic subjects. It was found that only 9% of the dose was deposited in the whole lung and 3% of it in the alveolated region. In a further study, a comparison was made with various extension tubes attached to the actuator. Deposition in the whole lung and on the conducting airways was significantly increased by the extension tubes, but the alveolar deposition remained unchanged. As the Teflon particles are insoluble, the physicochemical difference between these particles and the particles of a drug substance should be taken into account.

After inhalation from a pressurized aerosol, indirect measurements can be performed in order to establish the availability of the drug substance into the airways. This can be determined as the difference between the amount delivered to the subject on the one hand, and the losses in the oral cavity and in the exhaled air on the other. Patterson et al. (1968) found that almost half of the dose of isoprenaline delivered from an inhalation aerosol could be recovered after rinsing the oral cavity. Such an indirect method does not suggest where the remaining deposition occurs in the airways. The difference in the metabolic pattern between orally and intrabronchially administered tritium-labelled isoprenaline was used in order to calculate that less than 10% of the dose delivered from the aerosol was absorbed directly by the lungs, whereas approximately 90% was swallowed into the gastrointestinal tract (Davies, 1978).

Indirect measurements were performed in order to investigate the deposition pattern after the inhalation of terbutaline through various tubes attached to an actuator (Morén, 1978a). The deposition of drug in the mouth could be significantly reduced by attaching

an additional tube to the actuator. The total loss of drug substance in the actuator, tube and mouth could be significantly reduced, indicating the possibility of increasing the availability of the drug to the airways. A small extension tube has been described by Sciarra and Cutie (1978). It is intended to be used for a pressurized inhalation aerosol containing triamcinolone acetonide. The extension was claimed to be effective in obtaining less deposition of drug substance in the oral cavity. Indirect measurements have also been performed to investigate the deposition pattern of terbutaline after the inhalation of pressurized aerosols with various vapour pressures and metering volumes (Morén, 1978b). In order to obtain a high availability of drug to the airways, the metering volume of the pressurized aerosol should be low and the vapour pressure high.

The fraction of the dose from a pressurized aerosol lost with the exhaled air seems to be negligible. Less than 1% was found in the exhaled air both after the administration of a freely water-soluble drug and a practically insoluble drug (Morén and Andersson, 1980). A particle growth due the moisture absorption did not appear to be important for the total drug deposition in the respiratory tract; still, a particle growth could influence the regional deposition in the respiratory tract.

Clinical evaluation

Bronchodilators are the drugs most frequently used for oral inhalation. There seems to be lack of correlation between the drug level in plasma and the therapeutic effect after aerosol administration. The main plasma peak appears much later than the peak activity, and it seems to originate mainly in absorption of drug substance swallowed into the gastrointestinal tract (Walker et al., 1972; Nilsson et al., 1976). The bioavailability in the lower respiratory tract of bronchodilators administered by inhalation can hardly be measured by means of the concentration in biological fluids, but well-controlled clinical trials in humans are considered to be sufficiently accurate (Federal Register, 1977). The activity is evaluated by various lung-functioning parameters. Such tests have frequently been used in comparisons involving a drug after various routes of administration, but there are rather few published trials comparing pressurized aerosols with different formulations or with different inhalation devices.

The acute clinical effects of terbutaline were evaluated on asthmatic patients using two different tubes attached to the actuator (Lindgren et al., 1980). The improvements of the lung function were greater when the attached tubes were used than with the actuator alone. Another study failed to demonstrate an improvement in bronchodilator response using an attached tube (Bloomfield et al., 1979).

The bronchodilating effect of terbutaline was investigated in asthmatic children using the actuator alone, or combined with a collapsible tube with a volume of 0.75 litres (Ellul-Micallef et al., 1980). Valves were adapted to the tube in order to control the air flow for inhalation and exhalation, allowing the aerosol cloud to be carried only by the inspiratory flow from the tube to the patient. When the tube was used, the improvement in lung function was significantly greater than when the actuator was used on its own. Inhalation by means of the tube allowed the children to use the pressurized aerosol without any help.

A 1.2 litre reservoir bottle with a one-way face mask attached to the end was used in administering beclomethasone dipropionate from a pressurized aerosol to children

(Freigang, 1977). In a follow-up study, all children were observed to have a good response (Freigang, 1980). There were no side-effects and a better utilization of the aerosol was obtained by the use of the special inhalation device.

Lately, much interest has been expended on the ability of adult patients to follow the instructions for the oral inhalation of pressurized aerosols (Coady et al., 1976; Orehek et al., 1976; Paterson and Crompton, 1976; Gayrard and Orehek, 1980). Even after training, many patients were unable to follow the instructions completely. However, no objective evaluation was made of the importance of each individual step in the performance. In the instructions to the patients, it is normally stressed that the pressurized aerosol should be actuated in the early phase of an inspiration. Bloomfield et al. (1979) studied a modified inhalation procedure, the dose of terbutaline being released 2 s before a deep inspiration. The results indicated that a therapeutic effect could be obtained even when the aerosol was actuated before inhalation. When a tube was attached to the actuator, the efficacy was similar to that occurring after actuation during the inspiration. The modified inhalation procedure was found to be useful for patients who had difficulties in synchronizing inhalation and dose actuation (Godden and Crompton, in press). Breath-actuated aerosols have been developed to overcome the difficulty of synchronization, but the therapeutic effect was not improved by automatic devices as compared with conventional actuators on trained patients (Thiringer, 1972; Coady et al., 1976).

The instructions to the patient on how to use pressurized inhalation aerosols have to a great extent been based on the known deposition of dusts in the respiratory tract (Task Group on Lung Dynamics, 1966). However, some basic deviations must be considered in comparison with dust exposure: (1) a continuous change in droplet size occurs, caused by the evaporation of propellants after the primary generation of the aerosol; (2) the initial velocity of the aerosol droplets is high, but a deceleration occurs due to air resistance; and (3) a bolus of drug is inhaled in one single inhalation.

It has been desirable to investigate the relevance of each step in the instructions to the patient. A basis can then be obtained on which to work out instructions which are as easy as possible for the patient to follow and which result in an optimum efficacy of the drug substance when it is inhaled. A systematic study was performed by Newman et al. (in press, b). It was found that the bronchodilating effect of terbutaline was significantly reduced as the air flow-rate at inhalation was increased from 25 to 80 litres min^{-1}. The better efficacy resulting from a slow inhalation flow-rate was probably due to an improved penetration of the aerosol particles into the respiratory tract. When the subject held his breath for 4 s after a slow inhalation, the improvement in lung function was smaller than after a 10 s breath-holding pause, but 20 s of breath-holding produced no additional benefit. When slow inhalations were followed by 4 s of breath-holding, an actuation in the beginning of the inspiration produced greater bronchodilatation than an actuation in the middle or towards the end. The results concerning the lung volume of aerosol release went against those of Riley et al. (1976, 1979). In the latter studies, the therapeutic effect of isoprenaline improved when the drug was inhaled towards the end of a deep inhalation as compared with the beginning of the inhalation. As the inhalation flow-rate was much lower, and the breath-holding pause was not stated, it is difficult to make direct comparisons between the studies.

Further work will be needed regarding the efficacy of pressurized inhalation aerosols

after various modes of inhalation. The instructions to the patient should perhaps be different for various types of drugs depending on their site of action.

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