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SOME FUTURE PERSPECTIVES FOR UNIT DOSE INHALATION AEROSOLS*

P. R. Byron
College of Pharmacy, University of Kentucky
Lexington, KY 40536-0082

ABSTRACT

Unit dose inhalation aerosols fail to achieve optimal lung deposition even though this can be achieved by dispersing 1-5 μm aerodynamic diameter particles in air. Dry powder generators require rapid inhalation for actuation and fail to deaggregate and release much of their powder charge because of high particulate adhesion forces. Conversely, pressurized metered dose inhalers (MDIs) fail because emergent propellant droplets are too large and travel too fast. The present unreliable dosimetry associated with the MDI stems from a desire to administer the whole of the metered dose. Rational design should concede on this point and concentrate on reducing primary droplet size and preventing emission of non-respirable large droplets. The loss of a constant proportion of each metered dose in the device and not

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the patient would be a major achievement. Improved inhalation dosimetry will facilitate future formulation developments designed to sustain local activity in the lung. This may be achieved by reducing particle dissolution rates in the airways.

INTRODUCTION

Interest in drug delivery via inhalation is expanding rapidly. While bronchodilators, steroids and antiallergics have been administered as aerosols for some years, advances in respiratory physiology and immunology are increasing the number of locally active compounds requiring aerosol administration (eg. antiproteases[1], antileukotrienes[2] and phospholipids[3]). The lung and nasal routes of administration seem, furthermore, to be logical choices as non-injection alternatives for new generations of peptides which have obvious intestinal degradation and absorption problems. Although the normal lung is known to possess its own protease activity, this is mainly intracellular and competing absorption kinetics are rapid[4,5].

Despite the rapidly expanding knowledge base due largely to non-pharmaceutical research (physiology, toxicology and aerosol science) in this area, there is little awareness of the pharmaceutical possibilities and constraints. Lung deposition from pharmaceutical metered dose inhalers is small (<10%) and variable[4,6,7]. Thus, a fairly earned reputation for unreliable dosimetry is usually attached all too readily to inhalation aerosols without bothering to investigate the changes which must be made to overcome these problems. It is not the purpose of this

publication to review the literature exhaustively. Rather to pinpoint and discuss the problems in order to highlight pharmaceutically important research areas. These should be distinguished from interesting but less pressing concerns. Hopefully, by employing a pragmatic approach, pharmaceutical science will be able to exploit drug administration via inhalation aerosol more fully than it has to date.

Numerous studies document the effects of the various factors influencing particulate deposition in the respiratory tract. The subject area is complex and made more so by considerations of disease, different modes of inhalation, the physicochemical nature, shape and density of the particles or droplets studied, methods of aerosol sizing and the presence of different degrees of aerosol polydispersity. In this literature however, the word "aerosol" is invariably given its true meaning -- that of a dispersion of particles or droplets in air. As far as this text is concerned, we will take a brief and pragmatic look at the deposition literature, neglect the effects of disease and ask the question "What characteristics should a pharmaceutical 'dispersion of particles in air' possess in order to optimize lung deposition?"

Surprisingly, the question can be answered; even so, an astonishing amount of confusing and sometimes inaccurate information exists in the pharmaceutical literature. The semi-empirical model proposed by Gonda[8] to account for mouth (as opposed to nasal) inhalation provides an excellent starting point.

This model describes aerosol deposition in normal humans. Deposition is considered in the oro-pharyngeal (M; mouth), tracheobronchial (TB; ciliated or conducting airways) and pulmonary (P; alveolar) regions. Because deposition models are usually used to predict events following nasal exposure to environmental aerosols, it is not commonly appreciated that pulmonary and tracheobronchial deposition fractions (mouth deposition is wasted) for particles in the optimal, 1-5μm size range, are dramatically enhanced when mouth breathing is considered. Lippmann[9] and some others[10,11] have published data, which enabled Gonda to modify the Task Group aerosol deposition model[12] to account for the large reductions in aerosol loss due to the nasal passages. Gonda's model broadly predicts deposition following oral inhalation of defined particulate systems. Figure 1 shows the likely deposition of 1-15μm aerodynamic diameter particles inhaled slowly at approximately 20 liter min^{-1} (slow inhalation is associated with reduced impaction efficiencies in the oropharynx[13]). The dashed line (theoretical total lung deposition = TB + P) shows that, even without breath-holding (normally practiced to reduce aerosol losses due to exhalation), deposition efficiencies >60% are possible for non-hygroscopic particles with aerodynamic diameters around 3μm. While hygroscopic systems may deposit higher in the respiratory tract because of rapid growth in size in the high humidity of the airways[14], it should be emphasized that Gonda's model (Fig. 1) is founded on firm experimental data. From a practical point of

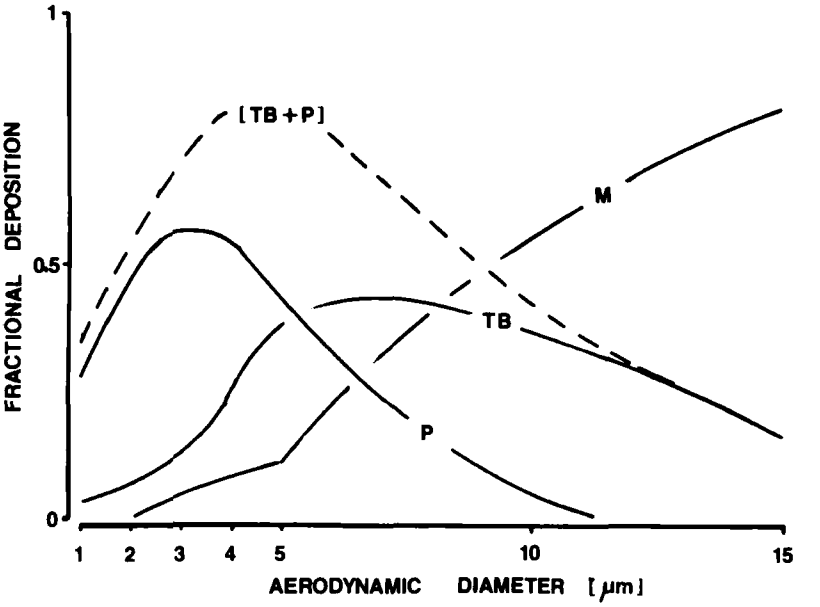

Figure 1

Fractional deposition versus aerodynamic diameter according to Gonda[8] for oral aerosol inhalation at 22.5 liter min^{-1} without breath-hold. Deposition is shown in mouth and oropharynx (M), ciliated tracheobronchial region (TB) and alveolar pulmonary region (P). The dashed curve (TB + P) shows total lung deposition. Enhanced deposition of the smaller 1-4 μm size range occurs in the lung if breath-holding is practised after inhalation[24].

view, aerosol researchers have proven that total deposition efficiencies between 30 and 100% occur without breath-holding for monodisperse aerosols in the 1-5 μm size range. Breath-holding is known to increase deposition of smaller particles which may otherwise be exhaled[12,13,24]. The lower deposition values shown

by the dashed curve in Figure 1 between 1 and 4 μm increase dramatically with breath-holding. Even for cases of significant polydispersity[15], high total lung deposition may be anticipated following inhalation of 1-5μm mass median aero- dynamic diameter (MMAD) systems. These statements contrast markedly with the typical <10% efficiency of pharmaceutical metered dose inhalers and dry powder generators. Why are pharmaceutical systems so inefficient? The answer is simple. Unit dose pharmaceutical systems are not aerosols in the true sense of the word. Furthermore, they do not generate aerosols with MMADs in the optimal 1-5μm size range for slow inhalation. Let us inspect these final statements in more detail. Because unit dose aerosols can be broadly categorized as either "pressurized metered dose inhalers" or "dry powder generators", the two types of system will be discussed separately.

PRESSURIZED METERED DOSE INHALERS (MDI's)

Figure 2a is a diagrammatic representation of the type of system used most frequently. Prior to formulation as a suspension in dry fluorocarbon propellants, drug is micronized so that the vast majority of particles have diameters <5μm. This is commonly accomplished by jet or "air impact" milling. Most drugs are hydrophilic and do not dissolve significantly in the hydrophobic propellants. Typical drug concentrations by weight may range up to ~1% so that fluid metering of say 25 - 100μL of suspension, commonly releases drug in around 100 μg quantities. Propellant mixtures vary somewhat although they all possess some common and

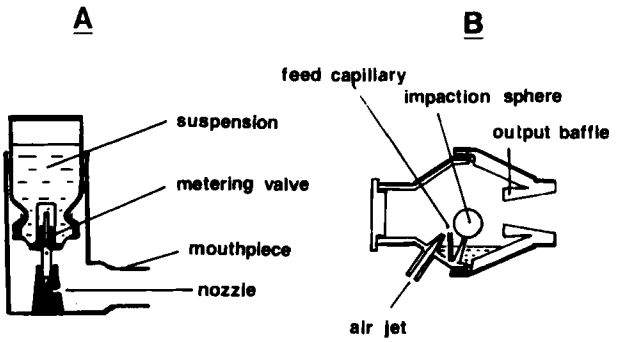

Figure 2

(A) Metered dose inhaler and (B) Micronebulizer. The latter is used for aerosolizing aqueous solutions prior to inhalation.

important characteristics. Blends of fluorocarbons 11, 12 and 114 are employed with vapor pressures equivalent to around 3.5 - 4.5 atmospheres (350 - 450kPa). Surface active materials such as sorbitan esters, oleic acid or lecithin are employed for suspending and, to some extent, valve lubricating purposes. If the product formulator and manufacturer have done good jobs, the product should be stable, easily and homogeneously resuspended and metered accurately and reproducibly in terms of suspension volume and drug dose following actuation.

In spite of all these efforts (and the fact that patients can be trained to inhale slowly and coordinate their inspiration with device actuation) >90% of each metered dose fails to reach the lungs of the patient[6]. There are several reasons for the suboptimal performance of pressurized MDI's. First, propellant droplets exit these devices at extremely high linear velocities

(25 - 50 $m.sec^{-1}$)[16] which, if actuation is straight into the oral cavity, is sure to result in high oropharyngeal losses due to impaction. Reducing propellant vapor pressure to reduce expulsion velocity is an impractical solution because droplet evaporation is then delayed and primary droplet size increased. Secondly, and probably foremost, the mean droplet size emitted from the actuator mouthpiece is typically in excess of 40 μm[17]. Thirdly, the propellants do not evaporate anywhere near as fast as was once supposed. While fluorocarbons 12 and 114 have sub-zero boiling points, propellant 11 is a liquid at room temperature, boiling at +23^{o}C[18]. Fluorocarbon 11 is incorporated at least 25% in all available suspension MDI's. The omission of the "low volatility" component would cause, at the least, severe valve operating difficulties. Following droplet emission from the mouthpiece (Fig 2a) therefore, a fairly rapid loss of the 75% most volatile propellants occurs. Because the volume of a spherical droplet is proportional to the cube of its diameter, this 75% loss should result in a reduction in mean size from say 40 to approximately 25μm. Mean droplet sizes 10 -25cm from the opening of the mouthpiece have been reported to be around 14 μm[17,19], a fact which may be due in part, to early sedimentation of large droplets from the aerosol cloud. In order then, to effect complete evaporation, and leave surfactant coated, micronized drug suspended in air, heat and time are required to remove the now supercooled, low volatility fluorocarbon 11. During this process, further losses occur due largely to sedimentation. Measurements of final mass

median diameters have been reported some 5sec after actuation which are consistent with the size of micronized powders originally placed in the suspensions (values <5μm)[20]. Two further complications should perhaps be mentioned at this stage. Supercooled droplets of propellant 11, in the humid environment of the airways[13,21], may act as condensation nuclei for water vapor. This may further delay droplet size reduction from MDI's. In some more concentrated non-aqueous suspension products, single propellant droplets containing more than one drug particle may be emitted. Although this final point has been treated in some depth[22] and drug powder aggregates certainly occur[23], this problem is insignificant given the present state of the art. Aerosols inhaled direct from actuator mouthpieces mainly consist of high velocity, large diameter droplets, most of which cannot possibly reach the airways.

Solving the "droplet size problem" is likely to be the way forward in order to control pulmonary deposition from MDI's. The obvious solution, that of eliminating propellant 11 from the formulations however, is not viable. Some lower volatility constituent is necessary for ease of manufacture and correct metering valve function. If we must live with the presence of such constituents, the most dramatic enhancement to MDI efficiency will come from reducing the primary droplet size emitted by the actuator. If, after all, the emitted size were 9, instead of 40μm, the droplet size following evaporation of low boiling point constituents would be <6 instead of 25μm! Six micrometers is

much closer to the size of the original drug particles as well as being almost ideal for deposition in the upper airways[24].

Some advantages of the MDI as it is currently manufactured are its size, simplicity, cheapness and disposability. It is not constructive therefore, to point to much more sophisticated aerosol generators which could do a better job. The typical air blast nebulizer shown in Fig 2b however, is not unlike the MDI in principle although typically, it emits aerosols of aqueous droplets with mass median aerodynamic diameters, MMAD <5 μm[25]. Non-aqueous aerosols generated by similar devices are usually even smaller in size [26]. The MDI (Fig 2a) usually "expands" the high vapor pressure suspension in the valve stem, throws it against a 90° bend and passes it through a nozzle. The atomizer or nebulizer shown in Fig 2b, blasts air or some other gas over the surface of a liquid at the top of the capillary delivery tube. A major difference between the two devices lies in the presence of the impaction sphere and output baffle in the second device (Fig 2b). The sphere causes further breakup of large droplets; the baffle prevents "non-respirable" large drops from escaping. These impact on the walls and return to the reservoir. In order to produce respirable aerosols, manufacturers of air-blast nebulizers accept that large droplets must either be mechanically broken down or removed from the output prior to inhalation. All similar devices produce some large droplets. Because a droplet's mass increases with the cube of its diameter, large, non-respirable droplets must be eliminated prior to inhalation.

Most importantly, this elimination should occur in the device and not in the patient. By varying formulations and metered volumes, employing disposable or washable baffles and screens in MDI actuators, we should aim to reduce the velocity and size of droplet output. Present unreliable dosimetry associated with the use of MDI's stems from the desire to administer the whole of the metered volume. Rational designers of the next generation of MDI's should concede on this point. Instead, they should concentrate on a) reducing aerosol droplet size and b) preventing emission of unwanted large droplets. In this way, we can hopefully not only improve, but also control, drug doses available for inhalation. Losing a constant proportion of the metered aerosol output in the device can hardly be considered a "waste" when for example, an oral dose of albuterol (4mg) is compared to the 180μg currently dispensed by double actuation of an MDI (approximately 20μg of which provides the therapeutic effect.)

EXTENSION DEVICES

Extension devices or "spacers" have been the subject of numerous recent investigations[27,28]. These small aerosol reservoirs are placed between the conventional MDI actuator (Fig 2a) and the patient. Aerosol is discharged into them immediately prior to, or at the same time as, inhalation. They are currently available from several companies and are probably here to stay in one form or another. The rationale behind their development has been:

1. The provision of extra time (and heat) to enable propellant droplet evaporation before inhalation.

2. The reduction of droplet velocity and impaction efficiency at the back of the throat, by spacing the actuator further from the mouth.
3. The provision of an "aerosol reservoir" for those patients who experience difficulties coordinating actuation and inspiration.

The incorporation (in some devices only) of a whistle or other audible device to inform the patient that they are inhaling too quickly (faster than approximately 20 L min^{-1})[28] is an extremely good idea. These could be built into existing actuators however and do not justify a "spacer" in their own right.

Extension devices are certainly a good idea. Even so, they do not compensate for inadequacies inherent in the MDI. The diagrams presented in Fig 3 summarize much of the work sponsored by Astra Pharmaceuticals to validate the "spacer" concept. If the values and sites of aerosol deposition are compared for usage of the "actuator alone" to "actuator with spacer", it is clear that for a model formulation, lung deposition can be enhanced and oropharyngeal deposition reduced by increasing the losses in the device itself[29]. Spacer-achieved reductions in oropharyngeal deposition have been advocated recently to lower the incidence of oral candidiasis resulting from the use of inhaled steroid aerosols. Even with a "spacer" however, high losses in the oral cavity occur (Fig 3), indicating that inhaled aerosol size distributions are still too large. It is time to employ these device mediated losses to ensure an appropriate aerosol size

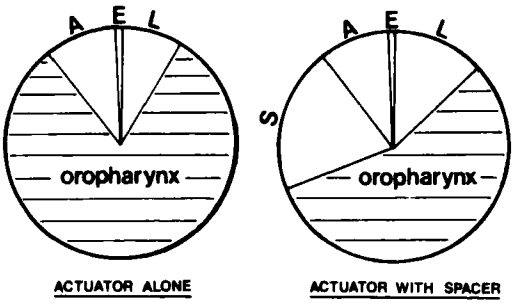

Figure 3

Typical mass deposition following inhalation by trained subjects of the aerosol output from an MDI with actuator alone and actuator with conical spacer[19]. When the spacer was used, oropharyngeal losses were reduced and small increases in airway deposition observed. Key: A = Actuator, E = Exhaled, L = Lung, S = Spacer.

distribution instead of, as we do at present, thinking of them as an unpleasant side effect which must be countered at all costs. With a rational actuator design employing baffles, it should be possible to emit a reproducible percentage of a previously metered volume as aerosol with a considerably reduced MMAD. Such aerosols have increased stability in reservoirs and deposit more reproducibly when inhaled[30,31,32].

DRY POWDER GENERATORS

Some locally active compounds are available for inhalation administration using either an MDI or a dry powder generator. These Spinhalers™, Rotahalers™ and others, should ideally aerosolize a fixed dose of previously micronized powder. This is usually packaged as the

required unit dose in hard capsules although in some cases, it may be mixed with inert diluents. Once the capsule is broken within the device, mechanical deaggregation of the powder is achieved as it passes through the blades of a fan activated by the patient's rapid inhalation[33]. Thus, the device only dispenses aerosol as the patient inhales, and in this way overcomes the coordination of actuation and inhalation problem experienced by some patients using MDI's[28,34]. Despite powder micronization to diameters <5μm however, a unit dose of a given locally active drug for dry powder generation is usually at least double that required from an MDI. By implication, if <10% of the dose reaches the lung from an MDI, <5% gets there using a dry powder generator. There are two main reasons why this is so. Firstly, to activate these devices and rotate the fan effectively, patients must inhale rapidly[35]. When particles are inhaled rapidly, they have increased inertia and are much more likely to impact at the back of the throat[13]. Secondly, micronized powders adhere extremely strongly to most surfaces they come into contact with; most especially themselves[36]! These forces are very difficult to overcome and there is a paucity of data in the literature concerning factors affecting them (especially for particles in the size range of interest). In one sense, complete deaggregation of powders can be achieved; incorporation of a powder in a fluidized bed of metal beads is effective for example[37,38]. Although in our experience a large proportion of the powder remains trapped in the bed, aerosol output has similar size characteristics to the original

powder[37,39]. Due to the high interparticulate forces which must be overcome to deaggregate powders however, the energy requirements to achieve reliable aerosol outputs from such devices are large. As a result, it is extremely unlikely that reliable inhalation aerosol dosimetry will be seen in the near future from devices relying, for energy input, on the patient's inspiratory effort. It is difficult to see how such devices can overcome the problems of producing a <5μm aerosolized powder for inhalation, without employing an additional high energy power source.

AEROSOLS FOR SUSTAINED LOCAL ACTIVITY

The previous text concerns deposition problems whether aerosolized drugs are intended for local or systemic activities. This section however, is designed to provide perspective on factors controlling duration of action within the respiratory tract itself. Means of achieving sustained bronchodilation for example, may not necessarily involve initial deposition of more drug than at present. Beta-adrenergic bronchodilators are extremely potent and function at concentrations as low as 0.001 μg ml^{-1} in isolated preparations[40]. Deposition of extremely small quantities in the airways will induce therapeutic effects. Isoproterenol is one of the most potent compounds. Its duration of action is short (~ 1.5hr) however, because of rapid metabolic deactivation by lung catechol-o-methyltransferase (COMT)[41,42]. Newer bronchodilators such as terbutaline and albuterol do not suffer this rapid local destruction and have durations of action in excess of 4hr after aerosol inhalation[40,41,42]. Because inhalation doses are orders of

magnitude smaller than those required to induce the same therapeutic activities orally or systemically, the main factor limiting duration of action from an aerosol is the length of time the drug is maintained at therapeutic concentrations in lung tissue. Elimination from the lung can occur by enzymatic breakdown, mucociliary clearance to the gastrointestinal tract and rapid dissolution and absorption[24,43]. Absorption of an aerosol dose is followed by dilution to therapeutically inadequate concentrations in the systemic circulation. Thus, in the absence of significant enzymatic breakdown, the main limitation to extended duration of these hydrophilic compounds appears to be their rapid dissolution and absorption. We recently reported fluorescein absorption half-lives in the region of 15min following its administration as solid inhalation aerosols in different sizes[44]. Lung absorption of xenobiotics proceeds without regard to pH-partition theory[45]. Small molecules (molecular weights 0 - 1000) are absorbed rapidly once dissolved[45]. The dissolution process for hydrophilic molecules can be extremely rapid, beginning even as they pass as solid aerosols down the high humidity environment of the respiratory tract (hygroscopic growth)[4,13,46,47].

The availability of a bronchodilating aerosol capable of easing respiration through an 8 hour sleep period would represent a major advance given, for example, the kinetic and toxicologic difficulties associated with theophylline therapy[48]. In the long term, to achieve this aim it is likely that new drugs will be syn-

thesized capable of increased sequestration in lung tissue. Some molecular requirements for high lung affinities have recently been reviewed by Hollinger[49]. A further possibility, provided that inhalation-compatible polymers are discovered, is that of covalently linked polymer-drug combinations which retain activity[50,51]. These may have increased durations due to their slower absorption or size-dependent airway retention[45]. In the short term however, it is more likely that formulation modifications will be used to decrease the dissolution rates of existing compounds and thus increase the duration of activity in the airways. From the many means of achieving release control, only two seem reasonable given the technical constraints which are already imposed on aerosol administration. For the solid, particulate systems used most frequently, these are either the administration of less water soluble drug forms or the use of biocompatible coatings which retard release. Methods such as matrix delivery[52], or others which involve the administrations of much larger quantities of excipient than drug, are inappropriate for aerosol administration. Even if toxicologic problems can be overcome with a chosen hydrophobic excipient, the technical difficulties associated with the need to increase deposited doses from aerosol systems are considerable.

Optimum release or dissolution rates of sustained release particulates are presently unknown. It is likely however, that these need to be much smaller than those commonly encountered with for example, oral sustained release products. Aerosols are

micronized systems which are deposited in minute quantities (10 - 100 μg) over a large mucosal surface area. Although this area varies with respiration, it is often quoted to be about the size of a tennis court (70 m^2)[53]. The depth of the mucus lining also varies, depending on the region being considered[54]. If, as a common approximation, it is assumed to be 2-5 μm deep however, the overall process can be likened to dissolving less than 1/10th mg of micronized drug in >100 ml of solvent. For a formulation to succeed, dissolution, not absorption, must become rate-determining in the systemic absorption process occurring from the respiratory tract[43]. Because airway dissolution kinetics for low solubility particulates are unknown, we are currently studying airway-to-perfusate transfer kinetics of fluorescein from sparingly soluble $Mg(OH)_2$ - fluorescein co-precipitates in isolated perfused rat lung[55]. These precipitates have variable intrinsic release kinetics up to 4 orders of magnitude slower than the dye itself[56]. Achieving such dissolution control in the viscous fluids lining the respiratory tract is probably less difficult than it initially appears. A low water solubility steroid is currently marketed as an aerosol for twice daily inhalation[57]. It is tempting to speculate that this low frequency of administration is attained by poor aqueous solubility and thus slow dissolution kinetics in the airways. Another group has recently claimed sustained bronchodilation in guinea-pigs following administration of a liposome-entrapped drug by inhalation[58]. Decreased drug release kinetics in the lung would appear therefore to offer some promise

as a means of extending local activity within the respiratory tract. Because of competing additional lung clearance processes (mucociliary and lymphatic transport) however, it is unlikely that durations beyond 12hr are possible following aerosol inhalation[43]. Nevertheless, physicochemical modifications to decrease aqueous drug solubility, and/or entrapment in low drug permeability, biocompatible coatings[58] are likely routes of advance for sustained action aerosol therapy in the future.

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