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PERSPECTIVES ON THE BIOPHARMACY OF INHALATION AEROSOLS*

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ABSTRACT

Particle size distribution is an important parameter with respect to the deposition behaviour of inhaled aerosols and must be viewed as a dynamic variable changing during the passage through the humid and warm environment of the respiratory tract. It is suggested that studies of particle growth rate and the formulation factors affecting it are necessary for a rational design of inhalation aerosols. Absorption and metabolism of drugs by the lung are also briefly reviewed and compared to the situation following gastro-intestinal administration. Possible advantages offered by the inhalation route are discussed.

INTRODUCTION

Biopharmaceutics may be defined as the study of the factors influencing drug release and subsequent absorption of an active principle from a pharmaceutical formulation. The presentation of a known dose at the site of absorption is often a trivial

problem. This is not the case with inhalation aerosols. It is necessary to first deposit the drug within specific regions of the respiratory tract before the biopharmaceutics of the dosage form may be studied. An adequate discussion of the factors influencing the efficacy of a drug presented as an inhalation aerosol must therefore include the processes preceding the release of the active principle. The biological response elicited by drugs released from aerosols (whether systemic or local[1]) may depend critically on their sites of deposition. Direct evidence regarding this matter is sparse in view of the technical difficulties involved[2]; in some instances, however, (the effect of inhaled allergens[3]) the picture is more definitive. Assessment of the therapeutic importance of localized deposition is particularly difficult in studies with bronchodilators where the pharmacological response is a complicated function of deposition, transport in the respiratory tract, absorption and dose-response relationships[2]. Whereas it is clear that inhalation aerosols must penetrate the respiratory tract (RT) at least to some depth to fulfil their therapeutic role, often more information is required about the sites of action before attempts can be made at targeting to a particular region[2]. The ultimate benefit to the patient in terms of reduced side-effects with, for instance, bronchodilator[2,4,5,6] or antibiotic[4,7] therapy in respiratory disease would appear to warrant more effort in this area. It has been suggested that the almost

total absence of inhalation aerosols intended for systemic action is probably due to the general lack of knowledge about the deposition of pharmaceutical aerosols[8].

DEPOSITION OF AEROSOL PARTICLES IN THE RESPIRATORY TRACT

As a result of the tortuosity of the respiratory airways, the particles (or droplets) must have an equivalent or mean aerodynamic diameter $D \lesssim 10\mu m$ to reach the tracheo-bronchial and pulmonary regions[9,10]. Large particles are deposited rapidly in the upper part of the RT by inertial deposition, and to a smaller extent at the branching points in the lower parts of the tract[11]. This process is sensitive to the mode of administration, rate of inhalation and geometry of the subject's naso-pharynx[9]. Solid particles deposited in this region are most likely to be carried rapidly upwards by the cilia so that they subsequently enter the gastro-intestinal tract (GIT)[8,10]. In the case of solutions, direct absorption competes with this process[9,10,11]. The depth of particulate penetration increases with a reduction in particle size. However, this is not parallelled by a monotonic increase in pulmonary deposition: particles in the intermediate range ($\sim 0.5\mu$) are sufficiently small to form "stable" aerosols which will be carried to the alveolar spaces by bulk motion of gas but they are neither large enough to deposit by gravitational sedimentation nor small enough to diffuse through stagnant air to the pulmonary surface[12]; hence, during normal breathing they will be largely exhaled. The

studies of Palmes et al.[13,14] have shown, however, that deposition of particles in this size range can be increased substantially during breath-holding, a maneouvre commonly practised by patients receiving medicinal aerosols. Indeed, if it is assumed that all particles penetrating beyond the naso-pharynx will be deposited during breath-holding, adaptation of the Task Group model[9] for non-hygroscopic particles suggests that as much as 95% deposition of 1μm particles in the lower lung can be attained[8].

Thus, optimisation of deposition requires the patient's co-operation: slow deep breathing and breath-holding aid penetration and retention of particles in the deep pulmonary regions[11], whereas rapid breathing should enhance inertial impaction of particles with D > 0.5μm in the nasopharynx.

PARTICLE GROWTH

Therapeutic aerosols are presented in the form of multi-component droplets, or soluble powders. Consequently, the particle size distribution may be expected to change due to condensation and evaporation during the passage of the aerosol through the warm and humid environment of the respiratory tract. This presents an additional problem to the formulator. The humidity in the lungs corresponds roughly to the vapour pressure above the isotonic tissue fluids[3] or, about 99.5% relative humidity (RH)[15]. An aerosol particle aims ultimately to reach a diameter at which its vapour pressure is equal to that of its

surroundings. This diameter is dictated by the vapour pressure depression due to the presence of solutes (Raoult's law) and the increased escaping tendency of water molecules from droplets as a result of the Kelvin effect[16]. The latter can be neglected usually for D > 1µm[17]. As an example consider a "typical drug" as a 1:1 electrolyte with molecular weight 360 Daltons, unit density and dry particle diameter of 5µm. Application of Raoult's law[9] shows that at equilibrium the droplet diameter will be 14µm. The possibility of such a dramatic increase in size is frequently neglected in formulation of and official standards for inhalation aerosols[8]. The importance of condensation growth for deposition clearly depends on the rate of this growth. An early indication that hygroscopic particles grow sufficiently fast in the RT to behave as droplets which reach their equilibrium diameters during the early phases of inhalation came from studies with NaCl aerosols[18]. These results were in agreement with Zebel[19] whose calculations indicated growth times for NaCl particles with an initial diameter of 1µm of the order of 1 sec. For smaller particles the growth takes place on a millisecond scale. More recent experiments[20] confirm the rapidity of condensation growth. It is thus unlikely that 'in vitro' lung models[11] may reveal much about the real behaviour of aerosol particles unless the environmental conditions in the respiratory tract are simulated[8]. Some authors prefer to calculate corrections for the model deposition

data obtained under ambient conditions[21]. It should be added that coagulation, which may also contribute to the dynamic changes in particle size distribution, is affected by the diffusive mass transfer between the droplets and the surrounding gas[22].

Byron et al.[8] placed a cascade impactor in a climatic cabinet at 37°C, and followed the changes in aerosol deposition as a function of RH. Instead of particle size analysis, they chose to study the changes in drug distribution between different droplet size fractions. This enabled them to overcome the problem of different growth rates of droplets of different sizes. Separation by the impactor occurred within the time range 1 to 5 seconds after aerosol generation. They calculated the dose fraction contained below a "therapeutic limit" of 5μm when the droplet environment was maintained at different relative humidities. The investigations showed that dramatic changes occurred in the dose fraction contained in droplets below 5μm equivalent diameter when RH was varied between 40 and 100% for propylene glycol: water and dry powder aerosols. Intal®, a powder mixture of sodium cromoglycate and lactose, showed that only 3% of the active principle existed as particles of D < 5μm at RH = 99% compared with 40% at RH = 85%.

Droplet growth rates depend strongly on the fluid dynamics of the aerosol[17], and this is known to vary from a turbulent to a laminar regime as one passes from the mouth to the highly

branched regions of the RT[23]. Deposition must therefore be affected directly by the nature of the airflow and indirectly by its effect upon the growth of individual droplets.

Experimental and theoretical information on the physicochemical behaviour of multicomponent polydisperse aerosols does not exist at present. Interesting phenomena may be expected to result from inclusion of surface active materials; the thin films which they form around the droplets have been found to retard droplet evaporation rates by several orders of magnitude[17,24]. Condensation, however, cannot be regarded as a simple reversal of evaporation because surface adsorption rather than diffusion through the film could be rate-determining[25]. There is some evidence that the hydrophobicity of the surface can affect droplet growth by condensation[26]. Further research in aerosol formulation may well make a substantial contribution to the control of their deposition within the respiratory tract.

DRUG ABSORPTION AND METABOLISM IN THE RESPIRATORY TRACT

Although a variety of drugs were found in the systemic circulation following inhalation therapy[4], quantitative data on drug absorption from the RT have appeared only recently.

Schanker and co-workers have been involved in a systematic study of drug absorption through the RT after intratracheal administration of solutions and inhalation aerosols to rats. They found that many common drugs, e.g., sulfonamides and anti-tubercular agents, are absorbed from the surface of the RT

rapidly by a passive non-saturable process; as in the GIT, the magnitude of the apparent oil/water partition coefficient (P) at pH = 7.4 plays a decisive role in this rate process except for compounds with extremely low P[27]. Chowhan and Amaro[28] found that 7-methylsulfinylxanthone-2-carboxylic acid was absorbed much more rapidly at pHs near and below its pKa than at higher pH, thus providing further evidence for the operational similarity between the pulmonary absorption barrier and other biological membranes involved in drug transport. These authors also found that, in analogy with the gastro-intestinal route, dissolution of solid particles may become the rate-determining step in drug transport from the pulmonary surface.

Properties of the alveolar environment with direct relevance to transfer of substances to the circulation have been recently reviewed[29]. It was suggested that the pH of the alveolar fluid is very nearly 7.4 and that the presence of components of this fluid capable of dissolving, chelating, precipitating or hydrolysing certain types of materials must be considered in future studies. The special role of pulmonary lymphatics in lung clearance has been reviewed by Lauweryns and Baert[30].

There are some remarkable differences however, between gastro-intestinal and pulmonary absorption. Para-aminohippuric acid and sulfanilic acid are absorbed by as much as two orders of magnitude faster from the RT (apparent absorption half-lives

70 and 45 min, respectively) than from the small intestine in the rat[31]. Nebulized drugs showed significantly reduced absorption half-lives when compared to administration of the same drugs as an intratracheal solution[32]. This may be due to occupation of a larger absorptive surface. It should be noted that this large surface area can, at least in principle, be reached by the nebulized drug within a few seconds[1]. This contrasts the situation found when the small intestine is used for drug absorption. Sodium cromoglycate, although practically unabsorbable from the GIT, has been found to be absorbed by a competitive, saturable, carrier-type transport from the RT[33]. Even very large molecules, such as intact albumin[34,35], insulin[36], dextran and inulin[37] are absorbed from the RT in significant quantities, possibly by pinocytosis[29].

There are several processes which contribute to the loss of drugs from the RT. Although parallel loss by metabolism or other processes could be responsible for a reduction in apparent absorption half-lives from the RT[38], in the experiments with polypeptides[34,36], intact molecules were found to be passed to the systemic circulation. This emphasises the lack of extracellular proteolytic activity in the normal lung; indeed, the presence of such proteases may lead to the development of pulmonary emphysema[39].

The pulmonary endoplasmic reticulum, originating largely from the bronchial epithelium and alveolar cells, is rich in

microsomes[40]. Their metabolic spectrum is similar to that of liver microsomes[41]. Certain differences between liver and lung microsomes have been found however. Lung microsomes for example, exhibit a comparatively low level of conjugation reactions[42].

One of the most important findings with regard to the development of new therapeutic aerosols is that of the considerable species variation in pulmonary metabolic activity[43]. This calls for careful extrapolation of data from animals to man, since pulmonary metabolism may contribute to, or prevent, the efficacy of drugs administered by this route.

CLINICAL SIGNIFICANCE

The ultimate goal of biopharmaceutical studies is to improve the therapeutic efficacy of drugs by optimization of the delivery system. Do inhalation aerosols offer any advantages over other, perhaps, safer routes[2]? One relatively unexploited characteristic of the inhalation route may well prove to be the rapid absorption offered by the extensive pulmonary surface. This aspect has been mentioned previously.

Optimization of the inhalation aerosol requires first that it becomes possible to deposit a known dose of drug in the desired part of the respiratory tract. Given such optimization, a case can be built for controlled administration of many drugs by this route. Drugs administered at present for their local effects within the RT could be administered more reliably and in

lower doses. Drugs which are inactive orally due to gastro-intestinal metabolism or hydrolysis, an extensive first-pass effect, or are merely poorly absorbed, could be offered with improved patient compliance in inhalation aerosols.

The rationale for the reduction of systemic side-effects by introduction of drugs to, or near the site of action, is well understood[44]. It may be expected therefore that the inhalation route would offer distinct advantages for drugs acting primarily within the respiratory tract. Salbutamol is a bronchodilator which probably exerts its anti-asthmatic effect locally in the RT[45]. Oral or I.V. administration of this drug, however, leads to many side-effects which are virtually absent when an equipotent dose is administered as an aerosol[6,46]. A corticosteroid aerosol - beclomethasone dipropionate - was found not to suppress the endogeneous secretion of corticosteroids in man when administered in its usual dose of 400 µg/day. The results were contrasted to the effects of a therapeutically equivalent per oral dose of prednisone[5]. Antibiotic aerosols have been recently advocated again for use in serious pulmonary infections, particularly when patients do not respond to parenteral therapy[7]. The absence or low serum levels following inhalation may be important especially for those antibiotics which cause severe systemic toxicity.

As mentioned previously, the anti-asthmatic drug sodium cromoglycate is well absorbed by a carrier-type mechanism from

the RT[33] but only very poorly absorbed from the GIT. Moss et al.[47] found that only 5 - 10% of the inhaled dose was actually absorbed. The finding can be interpreted in the light of experiments by Byron et al.[8] who showed that the respirable dose fraction (<5μm) was probably very small at relative humidities approaching the conditions in the RT. Because bigger particles are deposited in the mouth[47], or the nasopharynx, and subsequently swallowed, the drug reaching the systemic circulation almost certainly derives from the fraction deposited in the tracheo-bronchial and pulmonary regions.

Both isoprenaline and sodium cromoglycate are inactive orally but exert their respective activities upon administration as inhalation aerosols. Both aerosols are largely swallowed, probably for similar reasons[49]. Isoprenaline however, unlike sodium cromoglycate, provides an example of a drug which is inactive orally due to metabolic differences between the gastro-intestinal and respiratory tracts[48]. This drug undergoes a conjugation reaction in the intestine which inactivates it. In the RT, such reactions are uncommon[42], and instead, O-methylation occurs to a small extent[48]. Davies[48] stated that the bronchodilator activity may in fact be due to the small amount of unmetabolized isoprenaline which appears in the systemic circulation.

In the last two examples, the choice of the inhalation route is necessitated by the inability of the GIT to transport

the active constituents into the blood stream and to the target sites. Insulin is both poorly absorbed and inactivated in the GIT. Inhalation of nebulised insulin solutions in man[36] indicated less than 10% efficiency with poor reproducibility when compared to intravenous administration. The response times to this insulin were however, found to be quite short. One may speculate therefore, that the poor results were due to the combination of inadequate breathing techniques and condensation growth leading to poor deposition within the RT. The absence of extracellular proteases and the ability of the RT to transport large polypeptides (see above) lend indirect support to this view.

Many other clinical investigations using aerosols have been reviewed by Dautrebande[4] and Muir[2] but these authors were concerned more with generation of aerosols than their formulation. Clearly, the two problems are complimentary: aerosols of sufficiently small size must be generated but this effort may be futile if the particles grow rapidly to several times their original size. Furthermore, the nature of the formulation may affect drug release within the respiratory tract and consequently the aerosol's therapeutic efficacy.

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