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REVIEW

Inhaled drug therapy for treatment of tuberculosis

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SUMMARY

The lungs have received attention as a portal for drug delivery in tuberculosis (TB) from researchers addressing diverse objectives. These include: (a) targeting alveolar macrophages that harbour TB bacilli; (b) maintaining high drug concentrations in lung tissue; (c) systemic delivery of potent or second-line anti-TB agents; and (d) delivering agents that may change the host-pathogen dialectic. Formulation design considerations for each of the above objectives differ in slight, but important ways. As distinct from vaccine delivery formulations, inhalations intended for drug delivery are presumed to require chronic and repeated administration of larger amounts of material. This review seeks to summarize the consensus on the ways and means available or under development, to deliver different anti-TB agents as aerosols for inhalation. These agents include drugs in current clinical use, singly or in combination, experimental chemical entities, siRNA against host molecules, and finally, drugs in clinical use for unrelated pharmacological action, as modifiers of the host-pathogen dialectic. The pharmacokinetics of drug bioavailability in the lung, the blood and other tissues following lung deposition of inhaled therapies are also addressed. Finally, considerations on efficacy studies of drugs administered through aerosol delivery are discussed.

1. The rationale for pulmonary drug delivery in tuberculosis

The lung is the primary, if not the sole, portal of entry for mycobacteria that cause TB. It has therefore been of interest since the 1950s to deliver drugs used in the management of TB through the same route.[1] Pulmonary drug delivery in TB was initially investigated in Russia, where issues ranging across drug selection, aerosol generation, clinical outcome and adverse effects were addressed.[2–8] However, that body of literature is not easily accessible. In recent years, there is renewed interest in formulating drugs for pulmonary delivery for reasons that remain significant. First, the lung mucosa represents a large surface from which drugs may be systemically absorbed into the bloodstream, without having to undergo hepatic first-pass.[9] During the process of systemic absorption from the lungs, drugs introduced into this organ are likely to provide early and high concentrations within it. This is advantageous if, as in pulmonary TB, the lungs are the intended target site of drug delivery. Second, lung macrophages are efficient at fulfilling their evolutionary role of phagocytosing material entering the lungs. It has long been established that macromolecular drugs[10] and particulate[11–13] or vesicular[14–16] drug delivery systems introduced into the deep lung are likely to be picked up by alveolar macrophages (AM).[17] Finally, it has been argued that uptake of drug delivery systems by infected macrophages effects rescue of the macrophage from 'alternative activation,'[18] enabling the elaboration of innate bactericidal responses that could help in killing or containing TB bacilli.[12,19,20]

2. Methods available for aerosol delivery of TB therapies

Aerosol generation and inhalation by human patients may be accomplished by any of three well-established methods in clinical use. The oldest method of aerosol delivery to the respiratory tract is by inhaling smoke, but anti-TB therapies do not lend themselves

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easily to this method. Nebulization, or the generation of a mist of droplets through the use of compressed air or oxygen has been in clinical practice for a long time, and is recently experiencing advances in technology.[21] This technique consists of dispersing solid or phase-separated drug delivery systems into droplets suspended in a small amount of medium. The patient is expected to inhale the mist through the nose and mouth (Figure 1A).

The most familiar technique of administering medication to the airways and lungs is the pressurized metered-dose inhaler (pMDI or MDI). Such a device uses an aerosol propellant and a dose-metering valve to regulate the egress of defined amounts of medication to the respiratory tract (Figure 1B).[22,23] The single major issue with pMDIs relates to the necessity of training the patient to coordinate inspiration and actuation of the device. Time-lags between emission of a spray of medicament from the device and the beginning of inhalation lead to wastage of a proportion of the emitted dose.[24] A spacer device that contains the spray and prevents it from dissipating, while allowing more time for the patient to inhale is often used to mitigate this loss.[25]

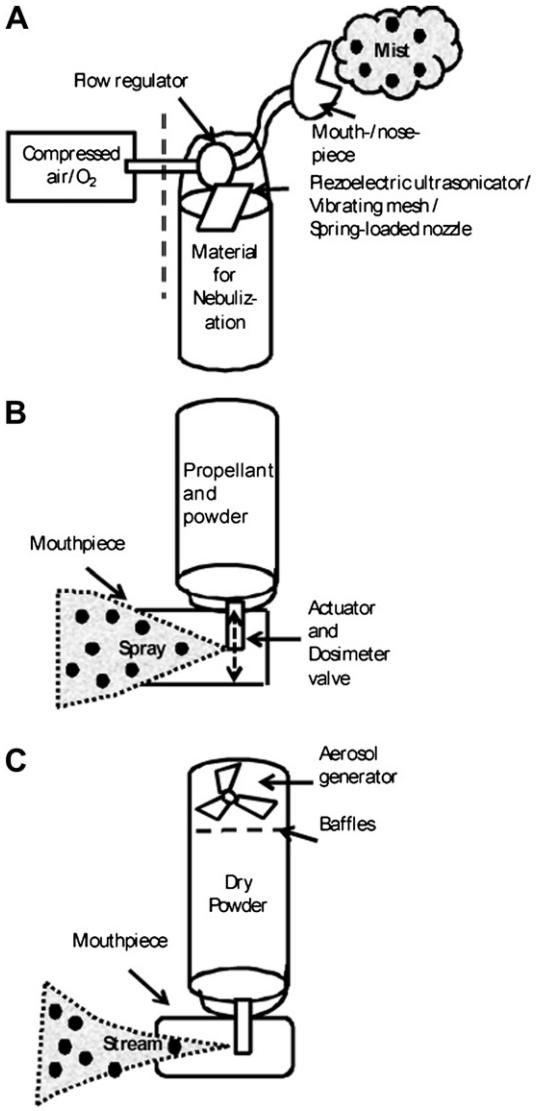

Figure 1. Schematic illustration of therapeutic aerosol delivery. (A) A nebulizer may achieve atomization of droplets by a stream of compressed air, or through piezoelectric sonication, or by mechanical means such as a vibrating mesh or spring-loaded nozzle. (B) A pMDI uses a dose-metering valve to deliver medicament suspended in a propellant spray. (C) A DPI delivers a more gentle stream of inhalant through indrawn breath.

Dry powder inhalers (DPI) represent an option that lies mid-way between nebulization of a medicament in an external aqueous or gaseous phase, and its delivery under positive pressure. DPI relies on the indrawn breath of the patient to pull in a dry powder (Figure 1C). The aerosol is generated by turbulence-creating devices actuated by the airstream of indrawn breath.[26]

In experimental animals, especially in studies on TB therapy, pulmonary delivery is often accomplished by intratracheal delivery. Various authors have reported on the instillation of small volumes of suspensions in the trachea of mice, rats and guinea pigs by endotracheal intubation. An increasingly-used approach for testing pulmonary delivery of drugs and vaccines in animal models is local/regional aerosol administration with a PennCentury MicroSprayer® (for liquids) or Dry Powder Insufflator™. These methods permit intratracheal administration of liquid aerosols or dry powders directly to the lungs. The tip of the device is inserted at the first bronchial bifurcation down the trachea of the anesthetized animal, bypassing the nose and throat and making it easier to precisely quantify the delivered dose. This is in contrast to MDI or DPI inhalers and/or nebulizers in animal studies, which filter the aerosol through the nasopharynx, are prone to inter subject variability and are not capable of targeting a desired, predetermined area of the lungs. However, studies using fluorescent particles as well as dyes have shown that the distribution of the thus applied formulations is mainly within the central lungs, with only a minor percentage reaching the alveolar space.[27–29]

Misra et al. have proposed the use of a “nose-only” exposure chamber that has been demonstrated to deliver reproducible doses in an animal biosafety level-3 setting.[30]

3. Design and process considerations for aerosol delivery systems

Aerosols are multicomponent systems, which exemplify the need for design approaches to facilitate rational development and guarantee their quality.[31] Multivariate statistical methods can be employed to design the process space for each of the major aerosol systems. Examples of input and output characteristics are shown in Figure 2 as they relate to the three major components of all pharmaceutical aerosol products, namely the formulation, metering and aerosol dispersion mechanism. Experiments can be conducted in which the variables in particle manufacture, for example, are evaluated.[32,33] The variables involved in particle manufacture can be adjusted to optimize the drug content, dissolution rate, particle size (mass median aerodynamic diameter, MMAD and geometric standard deviation, GSD), emitted dose (dose delivered from the device) and fine particle dose.[34] The fine particle dose is the proportion of the total dose below a defined particle size related to the cut-off for entry into the lungs.

The complexity of pharmaceutical aerosol products contributes to considerable regulatory oversight and compendial quality and performance standards. The foregoing considerations require products to meet release specifications reproducibly and at minimum expense in terms of time, resources and cost. These are important elements in the development of commercially viable products in general, and especially in the context of products for the treatment of diseases of poverty with regard to the ultimate viability of the product in the country of use.

4. Formulation

Numerous papers are available in the literature on formulating inhaled therapies for TB, but no anti-tubercular inhalable