INHALATION AEROSOLS

PHYSICAL AND BIOLOGICAL BASIS FOR THERAPY

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Medical Devices for the Delivery of Therapeutic Aerosols to the Lungs

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I. Introduction

Despite the numerous methods that can be employed to generate aerosols in therapeutically useful size ranges and concentrations (Chapters 9–11 and 13), only three basic aerosol delivery systems have found their way into commercially marketed drug products. Specifically, these are metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers. These three classes of devices do not represent optimal delivery systems in terms of their ability to produce monodisperse aerosols that can be precisely dosed in a single breath, but rather are examples of delivery systems that achieve minimally acceptable characteristics in a simple, convenient, inexpensive, and portable format. To be acceptable for clinical use, an inhalation delivery system must meet certain criteria:

1. It must generate an aerosol with most of the drug carrying particles less than 10 μm in size, and ideally in the range 0.5–5 μm, the exact size depending on the intended application.
2. It must produce reproducible drug dosing.
3. It must protect the physical and chemical stability of the drug.

4. It must be relatively portable and inconspicuous during use.
5. It must be readily used by a patient with minimal training.

These minimal requirements alone do not guarantee commercial success. Most commercial products currently under development aim to provide multiple dosing (typically 200 doses) with minimal excipient inhalation (which can lead to poor organoleptic properties in the mouth, and oropharyngeal irritation). Patient convenience, competitive manufacturing costs to MDIs, and added value features, such as dose counters or an indication of appropriate inhalation flow rates, are also considered desirable. In this chapter, the components, designs, and operating conditions of typical inhalation products are discussed, together with the possibilities that could be realized by "next generation" aerosol delivery systems.

II. Metered Dose Inhalers

Since the 1950s, MDIs have been the mainstay of inhalation therapy, ostensibly because they were perceived to meet most of the criteria outlined above. However, over the years a number of deficiencies have been identified. Only a small fraction of the drug escaping the inhaler penetrates the patient's lungs (1,2) due to a combination of high particle exit velocity and poor coordination between actuation and inhalation. The unstable physical nature of suspended drug particles in propellant, combined with suboptimal valve designs, has led to reports of irreproducible dose metering following a period of rest (3). Low concentrations of potentially carcinogenic compounds were found to be extracted from valve components by the propellant system (4) and inhaled by the patient. However, the largest threat to the continued availability of pressurized MDIs is their dependence on chlorofluorocarbon (CFC) propellants, which have been linked to the depletion of stratospheric ozone and are now scheduled to be phased out under the terms of the "Montreal Protocol on Substances that Deplete the Ozone Layer" (5,6). Despite these concerns, new device designs, improved formulations and valves, and a switch to "environmentally friendly" propellants are likely to keep the MDI in common use.

The modern MDI shown in Figure 1 is little changed from its predecessors, and contains the same three basic ingredients: drug, one or more propellants, and in most cases, a surfactant. A liquefied propellant serves both as an energy source to expel the formulation from the valve in the form of rapidly evaporating droplets and as a dispersion medium for the drug and other excipients. A surfactant is typically present to aid with the dispersion of suspended drug particles or dissolution of a partially soluble drug, and to lubricate the metering value mechanism. In some formulations

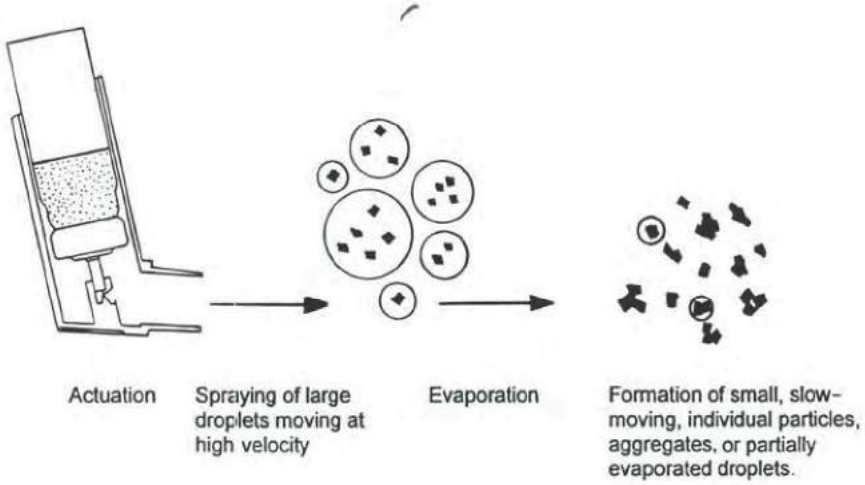

Figure 1 Diagram of a typical pressurized metered dose inhaler showing mechanism of particle formation.

a surfactant is reported to be unnecessary (7). Drug can be dissolved in the liquefied propellant/surfactant combination, with or without the aid of a less volatile cosolvent (8,9), or suspended in the form of micronized particles (10). In all currently marketed formulations, drug dissolution necessitates the use of an ethanolic cosolvent. Flavors (such as dissolved mint extracts) and suspended sweeteners (for example, micronized saccharine) may be present to combat the unpleasant taste associated with significant oropharyngeal deposition following inhalation. To enhance chemical stability, antioxidants (ascorbic acid) or chelating agents (EDTA) may be present in formulations in which the drug is dissolved.

The popularity of traditional CFC propellants has stemmed from their low pulmonary toxicity, high chemical stability and purity, and compatibility with commonly used packaging materials. In addition, they are nonflammable. Combinations of the three most widely used CFCs, trichlorofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12), and 1,2-dichlorotetrafluoromethane (CFC-114), are typically combined in varying ratios to achieve a desirable combination of vapor pressure, liquid density, and solvency (11). Following a long search for alternative propellants with similar characteristics to CFCs, 1,1,1,2-tetrafluoroethane (HFC-134a) has emerged as the primary replacement, and commercial formulations containing this propellant have recently gained or are awaiting marketing approval in several countries (12). In addition, 1,1,1,2,3,3,3-heptafluoropropane (HFC-227) is being actively investigated. In the recent past,

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