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The Design and Development of Inhalation Drug Delivery Systems

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INTRODUCTION

The inhalation delivery of therapeutic agents has been known, though poorly understood, for many years. A wide variety of agents has been administered to the lung via oral inhalation, for the treatment of diverse disease states. The most frequent use of inhalation therapy is for the treatment of obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD), using drugs such as short- and long-acting β sympathomimetics, corticosteroids, and anticholinergic agents. However, the respiratory route has been receiving increased attention since the early 1990s as a portal route for systemic drug delivery, most notably for the delivery of inhaled insulin [1,2].

Common to all inhalation dosage forms and delivery systems is the need to generate the optimum "respirable dose" (particles $< 5.0\,\mu m$) of a therapeutic agent, and this is a central performance feature in the rational design and selection of a delivery system. Moreover, this performance, in terms of aerosol

quality, should be demonstrated throughout the product's shelf life, in addition to the more usual chemical and physical stability criteria. Thus, particularly in the development of metered-dose inhalers (MDIs) and dry powder inhalers (DPIs), device design is integrated with formulation work in the overall product development strategy. Frequently, therefore, such inhalation delivery systems tend to be compound specific. Thus, the physicochemical properties and the pharmacological profile (dose) of a given compound will occasionally predispose the choice of inhalation system. Hence, a good basis of preformulation information is essential for the rational design, selection, formulation, and development of inhalation drug delivery systems.

Within the pharmaceutical industry, inhalation drug delivery system selection is a pivotal commercial decision. This should be based on factors such as:

Overall clinical objective (acute or chronic treatment)
Target patient population (e.g., ambulatory, infants, elderly)
Regulatory requirements
Competitor activity

Three basic types of commercially available inhalation drug delivery systems exist, and each is specifically addressed in this chapter.

Nebulizers: Traditionally used for the acute care of nonambulatory, hospitalized patients, particularly with coordination or dexterity difficulties. Solutions or suspensions can be nebulized by ultrasonics or an air jet and administered via a mouthpiece, ventilation mask, or tracheostomy.

Metered-dose inhalers: A versatile, multidose inhaler where the drug is formulated in a propellant mix, under pressure, with the drug being expelled (by a valve) in a metered volume from the volatile mixture as the propellant evaporates. These products have been the subject of much research interest since the early 1990s as pharmaceutical companies have sought to replace their CFC formulations with newer formulations containing the non-ozone-depleting gases (hydrofluroalkanes—HFAs).

Dry powder inhalers: These are inhalers that typically fall into two general types of commercially available systems: single-dose and multidose systems. The multidose systems have been finding increased use in recent years and are generally either "passive" devices, where the patient provides the energy to disperse the drug powder in a stream of inspired air, or "active" devices, in which the energy comes from the device.

This chapter presents an overview of formulation design, describes device function, and addresses product operation in relation to inhalation delivery system performance for nebulizers, MDIs, and DPIs. Methods of manufacture of dosage form are also briefly discussed to highlight critical features of each inhalation delivery system.

PREFORMULATION ASPECTS ON INHALATION DRUG DELIVERY SYSTEM DESIGN

Due to the diverse nature of inhalation dosage forms, preformulation as applied to the development of inhalation formulations can be extremely broad in scope. Although a good deal of relevant information of a generic nature (i.e., pK_a, log P) would typically be generated during preliminary physicochemical profiling of a drug substance [3], specialized information specific to the intended dosage form is also required.

The importance of identifying the mode of delivery to the lung (i.e., nebulizer, MDI, DPI) as early as possible cannot be overemphasized. A drug salt form selected assuming development of a propellant-based MDI suspension formulation may be wholly unsuited for application in an aqueous-based nebulizer suspension on the basis of solubility and crystal growth potential. Physicochemical properties and stability issues considered to be of importance in the development of inhalation formulations are discussed later, as they relate to the individual dosage forms.

Particle Engineering

Since the early 1990s, the notion of producing particles of a specific size, density, and morphology has evolved, and it has the potential to lead to significant advances in pulmonary drug delivery [4]. Typically, particles for use by inhalation would be produced by a milling (micronization) process that would result in a batch of material with a size range between 1.0 and 3.0 microns (necessary for inhalation). Scientists have realized that there may be more elegant techniques available for the production of small particles, including supercritical fluid recrystallization, spray-drying, or controlled precipitation, in which size control could be achieved and other desirable properties (e.g., extended release of the drug) may be realized [5]. There are a number of companies that have developed specialist processes to manufacture these types of particles (e.g., Alkermes; Eiffel; Nektar Therapeutics). These methods now provide formulators with the capability to have small quantities of material in a defined particle size readily available.

Formulations for Nebulization

The development of a nebulizer solution or suspension formulation is contingent on the same core preformulation data as would be required to support the development of any formulation. Physicochemical parameters such as pK_a, log P,

isoelectric pH (proteins and peptides), and solubility (vs. pH, ionic strength, buffer, and cosolvent level) are all important. Tonicity and solution pH, though typically regarded as formulation issues, must be investigated during preformulation to ensure selection of an appropriate salt form for development. For example, acidic (pH < 2) hypertonic and hypotonic aerosols have been demonstrated to induce bronchoconstriction in asthmatic subjects [6]. A hydrochloride or sulfate salt of a weakly basic drug that forms a strongly acidic solution, therefore, may not represent the optimum choice if the tonicity of the formulation is compromised as a result of pH adjustment using buffers.

It is important to profile the solution stability of the drug candidate as early as possible to identify the pH of optimum stability. The influence of light, oxygen, and trace metals on compound degradation also needs to be considered to assess the requirement for antioxidants (sodium metabisulfite, ascorbic acid, etc.) or chelating agents (EDTA, citric acid, etc.). Inclusion of such agents, though required to improve the chemical stability, must be weighed against the potential for adverse effects on the lung. Drug stability in solution should be monitored using a stability-indicating assay, following stress storage as a function of elevated temperature. In addition, conditions that promote hydrolysis (pH extremes), photolysis (ultraviolet and visible light), oxidation (O_2, O_2/light), and trace metal ion catalysis (Fe^{+2}, Fe^{+3}, Cu^{+2}, Co^{+2}, etc.) all merit consideration [3]. Temperature cycling is also useful as a means of assessing potential problems relating to complexation or hydrate formation as manifested by precipitation or crystal growth.

As a guide to formulation development, studies should be undertaken to evaluate the contribution of candidate excipients, including preservatives, antioxidants, chelating agents, cosolvents, and buffers on compound stability and solubility. This is particularly important in the development of suspensions for nebulization. Compatibility with packaging components also needs to be considered as a matter of priority. Peptides and proteins in particular are notorious in their ability to adsorb onto a variety of surfaces, particularly plastic.

Dry Powder Inhalation Formulations

Of critical importance in the development of DPI products is the evaluation, optimization, and control of flow and dispersion (deaggregation) characteristics of the formulation. These typically consist of drug blended with a carrier (e.g., lactose). The properties of these blends are a function of the principal adhesive forces that exist between particles, including van der Waals forces, electrostatic forces, and the surface tension of adsorbed liquid layers [7]. These forces are influenced by several fundamental physicochemical properties, including particle density and size distribution, particle morphology (shape, habit, surface texture), and surface composition (including adsorbed moisture) [8]. In addition,

the combination of dry powder formulations and plastics poses the additional problem of offering electrostatically charged surfaces for collection of drug particles. Interparticle forces, which influence flow and dispersion properties, are particularly dominant in the micronized or microcrystalline powders required for inhalation therapy (< 5 μm). It is obvious that the particle size distribution of the drug and the diluent (excipient) need to be optimized during early preformulation and formulation development studies to ensure consistent aerosol cloud formation.

It is imperative, during early development, to characterize the moisture sorption and desorption attributes of the drug in relation to available salt forms. Assuming solubility is sufficient to ensure adequate absorption, a nonhygroscopic form should be explored. This would confer a number of advantages, including improved flow properties and dispersion as well as enhanced physical stability in the bulk and final dosage forms due to minimal moisture transfer between the drug, immediate container (e.g., gelatin capsule shell), and the environment. Furthermore, improved chemical stability may result in the case of hydrolytically labile drugs. Hygroscopic growth during administration would also be minimized. Although inherently attractive, the approach of using nonhygroscopic drug forms must be applied with caution, because, in the case of insulating particles, the level of adsorbed moisture may not be sufficient to dissipate attractive electrostatic forces, resulting in particle adhesion. Particle morphology, including attributes such as crystal habit, surface texture, and porosity, also influences particle adhesion [9]. Anisometric particles, that is, those with extreme "elongation" or "flatness" ratios, tend to build up packing of high porosity, but they are also more readily deformed by compression than packing of isometric particles. Anisometric particles tend to align along their long axis during flow and, thus, to exhibit less internal friction than isometric particles [8]. Powder flow tends to be adversely affected by surface roughness and porosity.

A particle engineering approach that has been the subject of much recent attention is one in which sub-unit-density particles are produced. These particles are attractive because it is the aerodynamic diameter, rather than any other measure, that determines the site of deposition for inhaled particles. The aerodynamic diameter is the characteristic dimension of a hypothetical sphere, of unit density, with an identical setting velocity (the velocity at which a particle moves downward when acted upon only by the force of gravity) to that of the particle in question [10]. Many pharmaceutical aerosol particles are spherical with density of 1 g/cm^3, most certainly in the case of liquid aerosols. For these particles, the aerodynamic and geometric diameters are equivalent. However, particles with other than unit density can be "respirable" particles even if their geometrical diameter is not 1–3 μm in size [11]. Thus, the aerodynamic diameter, rather than the geometric diameter, must be given careful consideration when predicting deposition efficiency of a given inhaled aerosol. The distribution

of sizes around the aerodynamic median size is also an important parameter in the efficiency of deposition [12].

The efficiency of dispersion, in the case of dry powder aerosols, relative to varying geometric diameters of the particles may also be an important factor. Specifically, dispersion requires the powder to overcome interparticulate forces binding particles in bulk powder and to become entrained as single particles in the inhalatory airstream. Interparticulate forces are dominated by the van der Waals force for particles in a respiratory size range. All other factors being equal, the van der Waals force will decrease as the geometric particle size increases (Fig. 1). Thus, in general terms, probability of deposition in the deep lung is at odds with efficiency of dispersion for dry powder inhalers. Sub-unit-density particles provide a means to decrease interparticulate forces due to their larger geometric diameters, while their aerodynamic diameter is still in the respirable size range.

It should be apparent, based on the brief overview just presented, that prediction of powder rheology based on the potential interplay of a number of physicochemical properties is extremely complicated. Instead, flow and dispersion properties are generally characterized using appropriate derived properties, including, but not limited to, angle of repose, bulk density, compressibility, and dustability. It is important to identify and control critical

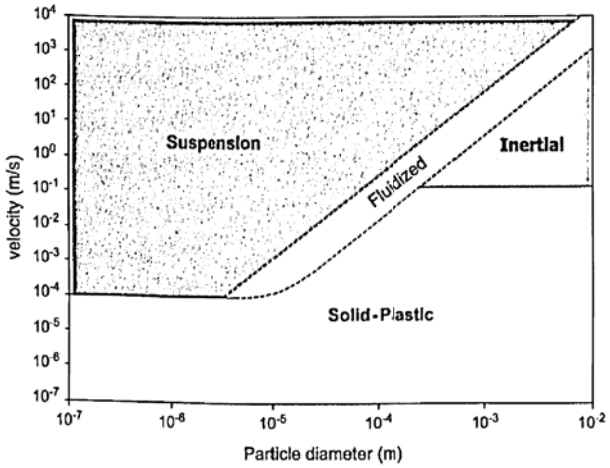

FIGURE 1 Phase diagram for typical granular material interactions.

parameters, both fundamental and derived, to ensure optimum and consistent product performance, although this may not always be possible [13].

Environmental factors, including temperature, humidity, and light, are essential considerations during formulation development. Therefore, it is imperative to evaluate the influence of these factors on the physical and chemical stability of the formulation during early preformulation studies. Light exposure can usually be controlled by judicious choice of product packaging; however, temperature and humidity are not so easily controlled, and they often act in concert to promote product degradation. The effects of elevated temperature and humidity on product stability can be assessed after stress storage. Some years ago Yoshioka and Carstensen [14] proposed several useful kinetic models for the accelerated testing of solid pharmaceuticals based on isothermal storage at controlled elevated temperature and controlled elevated humidity. Temperature- or humidity-cycling experiments can also be useful, particularly for assessing potential physical changes.

Chemical degradation after stress storage is assessed using an appropriate stability-indicating assay. In addition, physical changes are evaluated using an array of techniques available to the preformulation scientist, including polarized light microscopy (aggregation, crystal growth), differential scanning calorimetry, infrared spectroscopy, x-ray diffractometry, solution calorimetry, thermogravimetric analysis, and hot-stage microscopy (moisture uptake, polymorph interconversion, pseudopolymorph formation). Stressed stored samples should also be evaluated for evidence of caking and discoloration.

Metered-Dose Inhaler Formulations

The development of MDI formulations requires the same core preformulation data as described previously. However, additional parameters must also be evaluated, including solubility in propellant vs. concentration and nature of dispersing agent, crystal growth potential (related to solubility), and, most importantly, suspension properties (sedimentation, redispersibility). These issues have been studied very carefully since the early 1990s as pharmaceutical scientists have gained further experience with the "new" pressurized gases HFA134a and HFA 227, which have very different physicochemical properties from the more widely used CFCs that they replaced. Issues relating to physical stability must be addressed early during the development of an MDI suspension formulation. In addition to dispersibility, of particular importance is the potential for the drug to undergo crystal growth. Because this process is solution mediated, the solubility of the active in prospective formulations must be assessed. The influence of crystal and salt form, propellant composition, and surfactant should be evaluated with the objective of minimizing solubility. Although no general rules apply, it is prudent to limit drug solubility to the range of low parts per

million to avoid significant problems with crystal growth for suspension formulations.

The solubility of a solute is a function of the particle size of the solute. Small particles, possessing high surface free energy, are more soluble than larger particles. The increase in solubility is dramatic for particles of less than one micrometer [15]. This phenomenon is particularly relevant to the development of MDI suspension formulations because the drug is present as a microfine, polydisperse powder. Preferential dissolution of smaller particles results in localized supersaturation and crystal growth after deposition on larger particles (Ostwald ripening). The propensity of the drug to undergo growth is typically assessed by cycling prototype formulations over a range of temperatures that the product is likely to be subjected to (e.g., 2°C ↔ room temperature ↔ 40°C). Samples are evaluated microscopically for evidence of crystal growth after a predetermined number of cycles. Other techniques, including differential scanning calorimetry, solution calorimetry, infrared spectroscopy, and x-ray powder diffraction, can be used to characterize changes in crystal form.

Water should always be regarded as a hostile impurity in propellant-based MDI formulations. Although only sparingly soluble in CFC propellants, it is much more soluble in the HFA propellants (typically 600–2200 ppm, depending on the propellant [16]), and water can act as a powerful cosolvent. As such, it can induce aggregation and catalyze processes described previously. In addition, it can promote degradation of hydrolytically unstable drugs. Because water cannot usually be rigorously excluded from MDI formulations, it is important to evaluate its influence on product integrity and performance [17]. Temperature-cycling experiments should be conducted on formulation prototypes as a function of added water.

From the standpoint of the number and diversity of excipients generally used, propellant MDI formulations are relatively simple formulations. The current technology comprises either propellant-drug-based formulations, suspension formulations that contain one or more solvents (typically ethanol) to aid the solubility of the surface active agents, or solution formulations using known excipients, including glycerol [18]. Excipient compatibility studies can, therefore, be extended at an early stage to include actual formulation prototypes. Factors to be considered as part of the excipient selection process include solubility, chemical and physical compatibility with the drug, and potential interactions with container and valve components. This issue is reported to have affected formulation development activities to the extent that internally coated canisters are now being used for some MDI products.

Chemical compatibility is appropriately assessed by evaluating drug and surfactant blends, using a stability-indicating assay, following storage at elevated temperature of prototype formulations. Potential interactions of the drug with prospective containers and valve components can be evaluated by comparing

assay results for samples stored at elevated temperature in plastic-coated glass aerosol bottles with corresponding results for samples stored in contact with prospective packaging components, including aluminum as well as intact or dismantled valves. The oxygen and water content of the test samples should be controlled to establish their role in drug degradation and to avoid misleading results.

Criteria considered so far in the selection of a suitable drug form for MDI development include drug solubility and excipient and component compatibility. In addition to these parameters, suspension properties need to be carefully considered in the selection process. These are discussed in more detail later in this chapter in the section on the development of MDIs.

INHALATION DRUG DELIVERY SYSTEM DESIGN—NEBULIZED DRUG DELIVERY

Nebulizers are widely used today for drug delivery to the respiratory tract and are particularly useful for the treatment of hospitalized or nonambulatory patients. Fundamentally, there are two general types of nebulizer systems, the ultrasonic and the air jet.

In ultrasonic nebulizers, ultrasound waves (Fig. 2) are formed in an ultrasonic nebulizer chamber by a ceramic piezoelectric crystal that vibrates when electrically excited. These set up high-energy waves in the solution, within

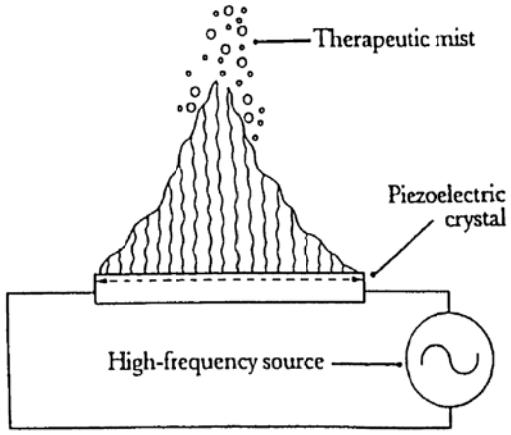

FIGURE 2 Schematic of an ultrasonic nebulizer.

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