Formulation Design of Dry Powders for Inhalation

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ABSTRACT: Drugs for inhalation are no longer exclusively highly crystalline small molecules. They may also be amorphous small molecules, peptides, antibodies, and myriad types of engineered proteins. The evolution of respiratory therapeutics has created a need for flexible formulation technologies to engineer respirable particles. These technologies have enabled medicinal chemists to focus on molecular design without concern regarding compatibility of physicochemical properties with traditional, blend-based technologies. Therapeutics with diverse physicochemical properties can now be formulated as stable and respirable dry powders. Particle engineering technologies have also driven the deployment of new excipients, giving formulators greater control over particle and powder properties. This plays a key role in enabling efficient delivery of drugs to the lungs. Engineered powder and device combinations enable aerosols that largely bypass the mouth and throat, minimizing the inherent variability among patients that arises from differences in oropharyngeal and airway anatomies and in breathing profiles. This review explores how advances among molecules, particles, and powders have transformed inhaled drug product development. Ultimately, this scientific progress will benefit patients, enabling new classes of therapeutics to be formulated as dry powder aerosols with improved efficacy, reduced variability and side effects, and improved patient adherence. J Pharm Sci 104:3259–3288, 2015

Keywords: inhaled by design; powder technology; engineered particles; amorphous; excipients; dry powder inhaler; aerosols; inhalation; protein delivery; pulmonary delivery/adsorption

INTRODUCTION

Dry powder inhalers (DPIs) have been providing effective treatments for patients worldwide for more than 60 years. Throughout this period, the fundamental principles of DPI formulation have remained unchanged. A drug is formulated as a powder in which the drug particles are sufficiently small for deposition in the lungs. The powder must be homogeneous on a scale commensurate with the dose, and homogeneity must be preserved during manufacture, shipping, and use. And, for passive DPIs, a patient's inspiratory effort must provide sufficient energy to fluidize and disperse the powder.

Although an inhalation product is commonly viewed as a drug and an inhaler, the formulation plays a critical role because it can influence both drug design and inhaler design. For example, most drugs for inhalation are small, highly crystalline molecules. Formulation technologies that relax or remove this constraint will enable development of a greater variety of drugs. Furthermore, formulation of a readily fluidizable and dispersible powder enables simpler device designs, benefitting both the manufacturer and, more importantly, patients. Although the drug substance, the formulated powder, the package, and the device are oftentimes discussed in isolation, inhaled drug product development requires integration of these technologies into the drug product. A holistic approach to dry powder product development requires that engineering of the drug substance and particle be performed with consideration of how the formulated powder will be filled, packaged, and ultimately delivered to a patient's lungs (Fig. 1).

What makes formulation of inhaled dry powders especially challenging is the diversity in molecule properties and delivery requirements. Drugs may be small molecules or macromolecules, hydrophilic or hydrophobic, soluble or insoluble, crystalline or amorphous. The site of action may be local to the lungs or in the systemic circulation, in the central lung or in the peripheral lung, intracellular or extracellular. Nominal doses may range from less than 10 μg to more than 100 mg, and delivered for either acute or chronic administration. And, for treatment of local lung disease, there is an overarching goal to increase the therapeutic index by improving targeting—increasing deposition in the lungs, reducing deposition in the mouth and throat, and maximizing residence time in the lungs.

The future of inhaled drug development is fueled by two key needs: formulation of diverse classes of drug substances and the continued need to improve the efficiency of drug delivery to the lungs. With the increased complexity in molecular design and the growing importance of biologics, drugs for inhalation are no longer exclusively highly crystalline small molecules. Although (low) delivery efficiency is not a concern for some drug classes, it precludes development of some drugs. Furthermore, improvements in delivery efficiency also reduce interpatient variability.

This review will focus on the four key aspects of dry powder formulation design: the nature of the drug substance, the nature of the particle, formulation approaches and excipients, and the integrated drug product. Formulation plays a critical role, enabling new classes of therapeutics to be formulated as dry powder aerosols with improved efficacy, reduced variability and side effects, and improved patient adherence.

DRUG SUBSTANCE CONSIDERATIONS

Drug Substance Constraints

Pharma has a strong preference for crystalline drugs. Most marketed respiratory drug products, including all therapeutics

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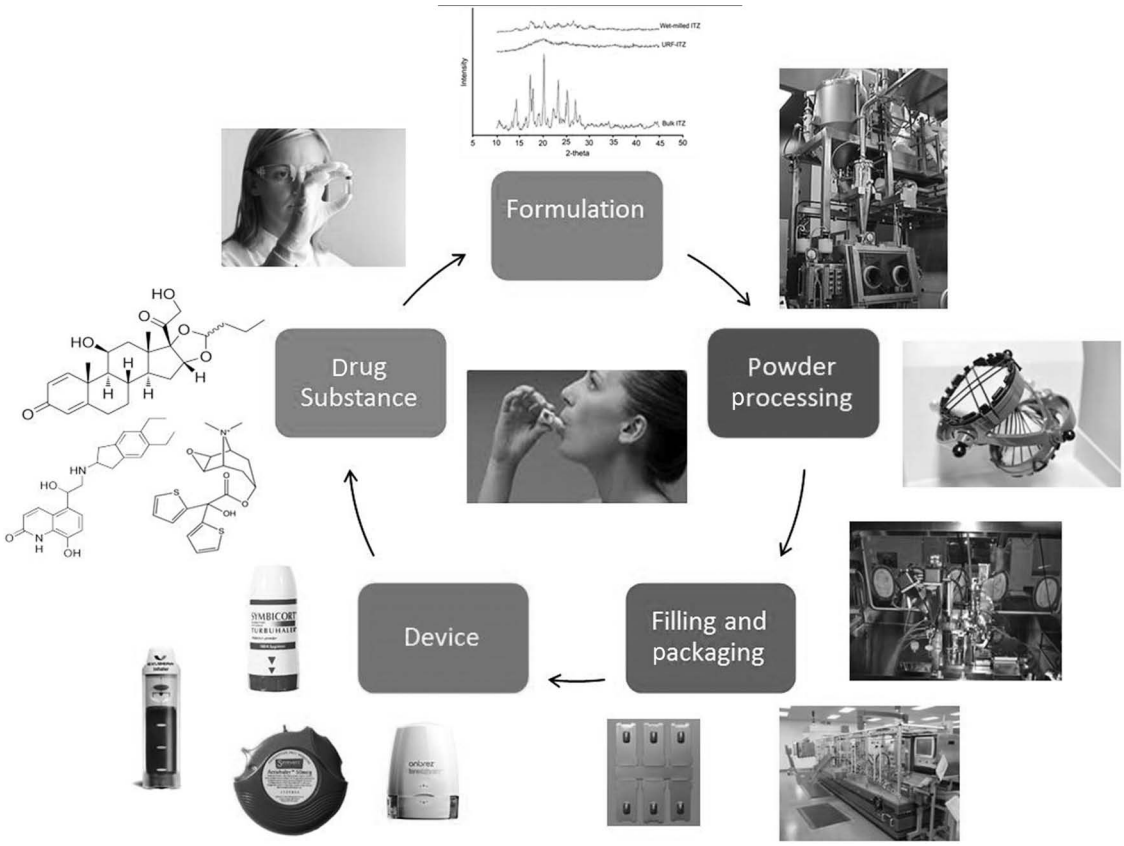

Figure 1. Formulation of a dry powder for inhalation requires integration of multiple technologies into the drug product.

for asthma and chronic obstructive pulmonary disease (COPD), are based on crystalline solids. Crystalline drugs tend toward a high level of purity and stability, particularly if the most thermodynamically stable polymorph has been identified. Drug molecules are generally designed with ionizable groups to enable salt formation. Salts are preferred because of their improved solubility, purity, and crystallizability relative to neutral forms. A number of salt-forming agents are screened in early development, with class I agents preferred. As a rule of thumb, the difference in pK_a values between the acid and base that form a salt should be at least three units.[1] Otherwise, the salt may have a tendency to disproportionate upon storage, yielding the neutral compound and an acid or base. Cocrystal forms have received increasing interest in oral drug delivery and will eventually also be developed for inhalation products.

An additional constraint for drugs for inhalation is that they often must be micronized to achieve particles in the respirable size range from 1 to 5 μm. The milling process can lead to a partial loss of crystallinity with the formation of amorphous or disordered material. Small amounts of such crystallographically defective material within a crystalline drug may have a deleterious impact on the formulated drug product in terms of both chemical and physical stability. Ahlneck and Zografi[2] suggested that most physical instability problems observed in pharmaceutical solids occur preferentially in the disordered noncrystalline regions. As a result, the drug substance must often undergo an additional deamorphization process to increase crystallinity[3]; a similar process is also used for carrier particles.[4] Also, for engineered blends, the crystalline drug substance must be chemically compatible with the carrier.

Although a small amount of amorphous material in a crystalline solid is generally unwanted, there are many instances in which formulation as an amorphous solid is preferred, particularly when the drug substance is amorphous. For example, dry powder formulations of proteins are generally prepared as amorphous solids.[5] Amorphous solids may be prepared by manufacturing processes such as spray drying in the presence of glass-forming excipients, which enhance the chemical and physical stability of the drug substance.[6–8] Many hydrophobic, small-molecule drugs with poor aqueous solubility and poor bioavailability can also be formulated as amorphous solids.[9] This tends to increase the rate of dissolution, thereby favoring cellular uptake and clearance of the drug.

Physical Properties of Marketed Respiratory Therapeutics

In their classic paper, Lipinski et al.[10] defined the molecular properties for a drug substance required to achieve the desired absorption, distribution, metabolism, and excretion (ADME) following oral administration. Their rule-of-thumb, referred to as Lipinski's "Rule of Five," followed from the observation that most orally active drugs are small and lipophilic. The Rule of Five states that an orally active drug should have no more than one violation of the following four criteria: (1) no more than five hydrogen bond donors (HBD); (2) no more than 10 hydrogen bond acceptors (HBA); (3) a molecular weight less than 500 g/mol; and (4) an octanol–water partition coefficient (log P) less than 5. Two studies explored the adherence of marketed respiratory drugs to the Rule of Five. Choy and Prausnitz[11] found that all of the 33 small molecule respiratory drugs they studied met the Rule of Five, with five of the drugs each

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