the penetration of aerosols into the peripheral pathways (83,84). A formulation adjuvant or pathological condition that alters the mucociliary mechanism of the respiratory apparatus can adversely affect drug deposition and absorption. Disease conditions that impair mucociliary clearance include chronic obstructive airway disease, asthma, cystic fibrosis, and bronchiectasis. Most of these conditions reduce mucociliary clearance of the lung. Absorption enhancers and preservatives are frequently found to cause mucociliary impairment.

4.3. Models for Assessing Systemic Drug Absorption After Pulmonary Delivery

Various in vitro and in vivo models for assessing pulmonary drug delivery are available for evaluating drug absorption from the lung or deposition of drug in the lung. Two inexpensive and widely used methods are the in vivo rat model and isolated perfused rat lung model. In vivo measurement of lung dose and deposition pattern can be studied by imaging and scintigraphy. Readers interested in methods for assessing in vivo lung dosing and deposition pattern of drugs in the lung are directed to two excellent book chapters by Clark and Borgstrom (85), and Everard and Dolovich (86).

4.4. Pulmonary Drug Delivery Systems and Devices

One of the most important requirements for inhalation drug delivery systems is that the delivery device and formulation are able to generate a respirable dose of therapeutics agent. Additional patient and formulation factors that should to be considered for rational design of pulmonary drug delivery systems include physicochemical properties of the drug (e.g., pK_a and $\log P$), drug stability, interaction with the device, and the potential for aerosolization. Additionally, the patient population, clinical objective, and regulatory issues are also important. The most widely used pulmonary delivery systems are nebulizers, metereddose inhalers, and dry-powder inhalers.

5. CONCLUSIONS AND IMPLICATIONS FOR PRECLINICAL DRUG DEVELOPMENT

This chapter illustrates the profound influence of formulation and administration route on the safety and efficacy of a drug candidate. An early understanding of the pharmacological site of action and the drug exposure profile that will produce efficacy with minimal toxicity is a paramount objective.

When possible, administration at or near the site of action is ideal. For example, this may be accomplished by dermal, pulmonary, or vaginal administration. If the site of action resides within an internal organ, a route of administration that maximizes systemic bioavailability should be considered. While the oral route would be implied by this need, other routes such