by the FDA. In addition, this sugar alcohol is also used as an aid for the diagnosis of asthma by assessing bronchial hyperresponsiveness (branded as Aridol or Osmohale depending on the country).

Likewise, a few inhalation powder antivirals have been developed, such as zanamivir (Relenza) for the treatment of flu caused by human influenza A and B viruses and ribavirin (Virazole) that is a synthetic nucleoside with antiviral activity against human respiratory syncytial virus.

As it was mentioned in Section 2, apart from the well-known benefits that the pulmonary route has in local therapies, this administration route also constitutes the portal of entry of drugs into the systemic circulation [19]. The deep lung provides higher bioavailability for macromolecules than any other noninvasive port of entry for systemic DD. Inhalation offers a noninvasive route for the delivery of three main types of drugs: (1) fast-acting small molecules such as fentanyl and loxapine with a molecular weight < 1000 Da; (2) peptides and proteins such as insulin, calcitonin, parathyroid hormone, growth hormone, luteinizing hormone-releasing hormone analogs, granulocyte colony-stimulating factor: and (3) vaccines such as those against measles and measles-mumps-rubella [20, 21].

In the past few years, the development of inhalable drugs with systemic effects has been a matter of great scientific interest. In 2006, the FDA approved Exubera (Pfizer), the first inhaled human insulin indicated for the treatment of type 1 and 2 diabetes. Despite its promising future, it was withdrawn from the market only after 1 year due to unexpectedly low sales. Several factors such as high cost of the inhaler, dosing-related issues, and large device size may have contributed to its failure [22]. However, in 2014, the FDA approved the second inhalation dry powder of ultrarapid insulin, Afrezza, that has been available in the market since 2015 at low costs.

Besides insulin, a few other biologics have been developed for pulmonary delivery. For example, Sinapultide, a synthetic peptide that mimics the human lung surfactant protein B, and Corusurf, a natural porcine surfactant, are both inhaled biologics indicated for the treatment of respiratory distress syndrome. In addition, an aerosolized recombinant human DNAse enzyme (Pulmozyme) was developed by Genentech as an inhalation solution for mucus depolymerization and clearance in CF patients, with significant improvements in lung function and respiratory symptoms.

In addition, several other inhaled drugs are commercially available to treat a variety of nonrespiratory diseases, such as levodopa (Inbrija) for Parkinson's disease, loxapine (Adasuve) for schizophrenia or bipolar disorders, and nicotine (Nicotrol) for nicotine withdrawal symptoms. The details of the inhalation products currently available in the US and EU markets are summarized in Table 4 [23, 24].

3.2. Patient Compliance to Aerosol Therapy

As it was well summarized by the Scientific Consultant Dr. Stephen Newman, DD to the lungs "is more complex than simply taking a tablet" [3]. Together with the inherent anatomical, physiological, and even pathophysiological barriers present in the respiratory tract (Fig. 1), the behavioral barriers of poor adherence and poor inhaler technique are still a challenge for patients, health care professionals, and the pharmaceutical industry. DD to the lungs requires to overcome two main key issues: (1) those related to the pharmacokinetic and pharmacodynamics profiles of the drug formulations and (2) those related to the patients' behavior and compliance (i.e., patients have to use an inhaler device and should use it properly). In the latter point, inhalation parameters such as inhaled flow rate, inhaled volume, and breath-hold pause should be successfully addressed. Hence, what patients do, fail to do, or refuse to do has significant clinical consequences. The state of the lung health and airway dynamics also affects the performance of DD systems in the lungs.

Strikingly, Borgstrom et al. reported that even with a correct inhaler technique, most inhalers deposit less than 20% of the inhaled dose locally in the lungs, and the remaining 80% is either deposited in the oropharynx and swallowed (pMDIs and DPIs) or deposited in the inhaler device (nebulizers) [25].

Unfortunately, in spite of the major research advances in the development of more effective DD devices with less oropharyngeal impaction and with drug formulations containing particles with smaller aerodynamic diameters, the patient's training for improved DD is an issue worth addressing related to both adverse clinical and economic consequences. In this regard, it was reported that almost 40% –70% of medical practitioners are unable to describe the critical steps to use inhalers effectively, and that almost US$5–7 billion of annual wastage is associated with inhalers' misuse [26].

As it was mentioned above, poor adherence to inhaled therapies is another common and significant problem that affects clinical outcomes [27]. Factors related to the inhaled regimen, the inhaler device, the patient's behavior and misconceptions, the health care professional's conduct, the social stigma for using an inhaler device, and other cultural issues are among the most common factors that affect the patient's compliance with aerosol therapy [28].