TABLE 3
Liposomal Formulations for Inhalation Present in Clinical Trials.

Liposomal Formulation	Clinical Condition or Disease	Phase
Liposomal trepostinil	- Pulmonary arterial hypertension	Phase I
Liposomal cisplatin (SLIT cisplatin)	- Osteosarcome metastatic to the lung	Phase Ib/IIa
Liposomal amphotericin B (Ambisome)	- Lung transplantation - Fungal infections - Allergic bronchopulmonary aspergillosis	Phase II/III
Liposomal cyclosporine A	- Bronchiolitis obliterans - Lung transplant rejection - Lung transplant complications - Chronic lung transplant complications - Lung transplant failure and rejection	Phase III
Liposomal camptothecin	- Metastatic or recurrent cancer of the endometrium or the lung	Not specified

attention not only in respiratory diseases, but also in vaccine formulations and in the systemic DD for the noninvasive treatment of pain, diabetes, and neurological diseases, among others. A great limitation to the development of novel SDR formulations using nanotechnology is that the number of FDA-approved excipients for inhalation is low, mainly due to toxicity issues.

3. MARKETED INHALABLE PRODUCTS AND PATIENT COMPLIANCE

3.1. Inhalable Drugs Commercially Available in US and UE Markets

In the past few decades, PDD has progressed significantly within the context of local treatment of lung diseases and for systemic use.

Currently, inhalable drugs appear as the best alternative for the treatment of chronic lung diseases such as asthma, COPD, bronchospasm, and CF. Most of these inhalation therapies were introduced in the market after 1987 and include inhaled corticosteroids (ICS) such as budesonide, fluticasone, flunisolide, and mometasone; short-acting muscarinic antagonists such as ipratropium bromide; long-acting muscarinic antagonists (LAMA) such as aclidinium bromide, glycopyrronium bromide, and tiotropium bromide; short-acting β_2-agonists such as salbutamol and terbutaline; long-acting β_2-agonists (LABA) such as salmeterol, formoterol, indacaterol, and olodaterol; and mast cell stabilizers such as nedocromil and sodium cromoglycate. The proven synergy of LAMA or LABA and ICS or LABA results in a fast development of combination therapies [16, 17]. For example, the inhalation powder Trelegy Ellipta is a combination of fluticasone furoate (ICS), umeclidinium (LAMA), and vilanterol (LABA), developed by GlaxoSmithKline and approved by the FDA in 2017. Furthermore, some of these combination therapies represented approximately 50% of the market sales in 2014; particularly, the combination of fluticasone-salmeterol (Advair or Seretide), the combination of budesonide-formoterol fumarate (Symbicort), and tiotropium bromide (Spiriva Handihaler) [2].

Recently, there has been an increasing interest in developing other inhalable drugs to obtain a direct effect on the respiratory tract. Among these drugs, antibiotics have had a special attention. To achieve their therapeutic effect in the respiratory system, these drugs should be administered at higher doses [18]. In this regard, a variety of antibiotics have been developed within the past few years to treat infections in CF patients. In 2012, Teva Pharmaceuticals received the European Medicines Agency's approval for the inhaled colistin Colobreathe, and 1 year later, Novartis received the FDA approval for the inhaled tobramycin Tobi Podhaler. Both products are high-powder dose antibiotics indicated for the management of chronic pulmonary infections caused by *Pseudomonas aeruginosa* in CF patients. Additionally, the FDA approved in 2018 the first medication for the treatment of *Mycobacterium avium* complex lung disease, the liposomal amikacin (Arikayce) that was in turn the first inhalation nanomedicine approved by the FDA.

Another inhaled drug for CF patients include mannitol that is traded by Pharmaxis with the brand name Bronchitol. Although this mucolytic drug is commercially available in Europe and improves lung function by increasing mucus clearance, it has not been approved