TABLE 4
Inhalation Products Available in the US and EU Markets Until February 2020—cont'd

Indication	Active Pharmaceutical Ingredients	Device	Brand Name (Manufacturer)
Diabetes	Insulin human	DPI	Afrezza (Sanofi Aventis)
Schizophrenia/ bipolar disorder	Loxapine	DPI	Adasuve (Teva)
Parkinson's disease	Levodopa	DPI	Inbrija (Acorda Therapeutics)

COPD, chronic obstructive pulmonary disease.

According to several studies, adherence declines when patients must take multiple daily doses and sometimes with different devices [29–32]. The patients' adherence may also be poor when they feel better; thus, they believe that they do not need the prescribed treatment, when they fear about its side effects, when they misunderstand the indications and the correct way to use the inhaler device, or simply when they forget to take medicine [33–35].

Health care professionals can also contribute to noncompliance by not teaching properly the inhalation technique simply because they do not know how to use the inhaler device properly [36, 37]. Hence, the phrase "training the trainers" fits accordingly. Health care professionals may improve the patient's compliance in different ways: (1) by choosing the proper device based on the patient's preferences and the prescribed medication; (2) by providing complete written and oral instructions on how to use the inhaler device properly, and preferentially they should give a practical demonstration; (3) by following up the patients; and (4) by education. Patients need to understand their disease, their therapy, and their inhaler device. The 10/90 rule for the successfully management of chronic lung diseases states that 10% of medicine and 90% of education are key points to ensure the clinical benefits of inhaled therapy [38].

4. THE ROLE OF FORMULATION FOR CONTROLLED PDD

Controlled PDD requires a first examination of the physiology and architecture of the lungs. One of the main aspects for a successfully controlled delivery is the overcome of lung clearance and the rapid drug absorption. The macro- and microstructure of the airways and the physics of the nano and micro vehicles are other critical points to be considered (fig. 3) [39]. Among them, the technology of inhaler devices, the nature of the materials, the crystalline state of the drugs, and the particle's size, shape, and surface charge are relevant parameters [40].

For example, particles with 5 μm or higher size are primarily deposited in the upper airways and throat and are most likely to be trapped by macrophage-type M1. Meanwhile, particles size of 0.5 μm and smaller are suspended in the air because of high Brownian movement and exhaled in large amounts. Having in mind these considerations, carriers in the size range of 1–5 μm are considered to be the most effective for PDD [41]. However, NPs of 100–200 nm are able to get deposited in the alveolar region in acceptable amounts. The main advantage of nanoobjects is the ability to be easily internalized by cells. In general, nanoobjects with an effective diameter $<$200 nm can be internalized by endocytosis mechanisms that involve phagocytosis and pinocytosis such as clathrin-mediated and caveolin-mediated endocytosis [42].

Numerous micro and NPs have been designed and studied for controlled and targeted DD at the lungs. For example, colloidal carriers (i.e., liposomes or SLNPs) show many other advantages as delivery devices because they improve drug solubility, provide a relatively uniform distribution of the drug in the airways, and show a controlled release profile. As a consequence, a reduction in dosing frequency could improve the patient's compliance and decrease possible side effects [43].

Regarding to the shape, spherical and spheroidal particles guarantee maximum surface when compared with other geometries of the same size and are easy to develop controlled release models and for scale-up. Residual positive charge of DD particles (i.e., by chitosan or polylysine coating) enhances the interaction within cell membranes by ionic interaction because they possess a negative residual charge [44].

The components of the formulation become a relevant tool to modify the microparticles' properties to