to coload a mucolytic DNase and the wide spectrum antibiotic levofloxacin. The microparticles could control the delivery of the DNase for 24 h and release the 30%–50% of the antibiotic in 3 days (Fig. 4, *bottom*). Administration to mice by inhalation demonstrated that microparticles deliver the antibiotic at least three times more efficiently than the free drug [54]. The developed systems provide new tools to improve the delivery and controlled release of the drugs to potentially enhance the current therapies known until the present.

Conjugation of drugs to polymers as PEG has also been described for the controlled release of proteins in the lungs as high protein loading can be achieved using this approach. In addition, PEGylation can enhance drug penetration across the mucosal barrier even through thick human mucus, such as in CF, and can promote entry into alveolar epithelial cells [7]. Other carriers described for the inhalational delivery of proteins or DNA included gelatin-, chitosan-, alginate-, PLGA-, PLGA-chitosan-, PLGA-b-PEG-based NPs, liposomes, and SLNPs.

Finally, there are some factors to be considered to develop a DD system for the treatment of chronic respiratory diseases [55–57]:

- NPs synthesized in the laboratory with established physicochemical properties such as size, surface charge, defined chemical composition including possible coating do not necessarily have the same parameters when are in contact with biological fluids and cells.
- Analysis of the interactions of nanocarrier-drugs.
- The activity of macrophages in all respiratory system can capture NPs annulling their therapeutic purpose.
- Minimal immune response to nanodrug administration [58].
- The presence of lytic enzymes in the lungs can affect the NP's stability and inactivate the drugs. Typical examples are budesonide, ciclesonide, fluticasone, and salmeterol [59, 60].
- Stability of the nanoformulations under different physiological microenvironments [61].
- Degradability of the carrier and characteristics of the degradation products.
- Toxicological analysis of the carrier and drug-carrier structure: immune effects, genotoxicity, and oxidative stress.

All these factors must be considered for the development of novel formulations as some aspects are conspiring against the proper delivery of drugs because they can reduce the effectivity of the formulations, changing the kinetic profile of drugs keeping out of the optimal therapeutic windows.

5. THE ROLE OF INHALER DEVICES FOR CONTROLLED PDD

Sometimes, unexpected Eureka moments occur as it happened in 1955, after Susie Maison, a 13-year-old girl who suffered from severe asthma, asked her father, a Riker laboratories' (now 3M drug delivery systems) vice president "Why can't you make my asthma medicine like mother's hair spray?" the answer to this question, the introduction of the first pMDI in the market, inaugurated a new era in the inhaler therapy with aerosols.

Aerosol therapy is the basis for the treatment of various diseases that mainly affect the respiratory tract such as COPD, CF, and asthma. To administer these drugs as aerosols, they must be generated from suitable inhalation devices such as pMDIs and their variants, DPIs, or nebulizers [19, 62–64]. Besides, novel inhaler devices have recently been developed to increase the efficiency of DD, such as SMIs. The drug is released by the gas or a driving force that acts as a vehicle to reach the respiratory tract, where it is deposited in a variable way, according to different factors. Therefore the efficiency with which these different inhaler devices deliver the active substance to the lower respiratory tract will depend on many factors that range from the intrinsic characteristics of the devices to the pathophysiological condition of the patient. Related to the device's characteristics, various issues are considered such as the physical form, the particle's size generated ranging between 1 μm and 5 μm for an optimal deposit in the lungs, the internal resistance, the final formulation, the velocity of the aerosol plume produced in the case of pMDIs, and the easy manipulation of the device, considering the coordinated action of the inhaler actuation with inhalation as one of the most important factors [65]. Table 5 summarizes the advantages and disadvantages of each type of inhaler device to understand the importance of the correct choice of each patient, taking into account not only the most effective medication to be prescribed, but also the correct device for that purpose. This, in part, will be determined by the mass of the drug (a few micrograms versus several milligrams) that is required to be delivered by inhalation. Hence, for doses of up to 1 mg, pMDIs and DPIs are suitable, but for larger doses, only some DPIs can be used. Nebulizers can deliver any drug dose, but for practical reasons, pMDIs and DPIs are most preferred for small doses, if it is possible [3].

5.1. pMDIs

pMDIs were developed in 1956 by Riker laboratories, and since then they have become the most popular and widely used inhalation devices to treat various