platinum drugs (cisplatin and oxaliplatin) remains a therapeutic option. Particularly, for those NSCLC patients who do not respond to the molecular targeted therapies or the immunotherapies or for those who acquired resistance and disease recurrence after targeted therapies or immunotherapies. In the past few years, DD systems, using nanotechnology, have been playing a critical role in the optimization of the chemotherapy used in cancer, including advances in inhaled therapy for lung cancer, such as liposome-encapsulated formulations of paclitaxel, doxorubicin, cisplatin, and 9-nitrocamptothecin. Some of these formulations rendered promising results and are currently under clinical trials (Table 3). Nanomatrix, niosomes, dendrimers, *n*-butylcyanoacrylate, and dextran NPs were also used for the development of aerosolized anticancer agents, either as monotherapy or combined therapy [111].

Finally, in the field of vaccinology, inhalation has also been tested as a noninvasive way of immunization due to the attractive immunological features present in the lungs such as the bronchial-associated lymphoid tissue and the local antigen presenting cells [112]. Few aerosolized vaccines were synthesized and are being tested for their efficacy and safety. For example, controlled release of NPs containing immunogenic tubercular antigens was prepared. It was observed that Poloxamer 407 and a CpG oligonucleotide can optimize the immune responses at least against *M. tuberculosis* antigen 85A, following pulmonary delivery [112]. The first live attenuated measles dry powder vaccine was successfully developed, and it is in phase I clinical trials [113]. Such dry powder vaccines are simpler to administer, do not need refrigeration and reconstitution, and ensure a good and long-lasting immunity.

8. CONCLUSIONS

During the last 30 years, PDD advanced significantly due to the continuous progress in aerosol science, device technologies, and nanotechnology. However, efforts are still strongly required to improve the patient's compliance and to improve the patient's quality of life and survival, especially in chronic pulmonary diseases such as asthma, COPD, CF, and tuberculosis or in poor prognostic malignancies such as lung cancer. The pharmacy industry is also moving toward the adoption of the potential advantages of the pulmonary route as a noninvasive and smart alternative to oral and parenteral delivery methods for the therapy of systemic diseases. The field of vaccinology was not excluded from the pulmonary delivery advances. In this regard, current progress in the pulmonary delivery of measles vaccine is ongoing.

In the past few decades, nanotechnology has impacted the world of medical science to an incredible extent that novel fields such as nanomedicine have emerged. Some nano DD systems are now in the market, and it is estimated to reach U$ 103 billion by 2023. The market of nanotechnology is blooming, and the field of PDD systems is moving rapidly, but not hand in hand with the inhaled nanomedicines. Since the approval of the first nanomedicine, Adagen, 30 years ago, only 50 FDA-approved nanodrugs are available for clinical use at present and of them only one for PDD, Arikayce (amikacin liposome inhalation suspension). However, several nanoformulations are under development or are undergoing clinical trials. This poor clinical translation of inhalation of nanomedicines is associated with the lack of a realistic view and understanding of the true limitations of nanotechnology, related to many pharmacokinetics and pharmacodynamics issues in humans that led to an overgeneralized and misinterpreted DD and drug targeting concepts such as the "famous" EPR effect for passive targeting into tumors observed in murine models but not in humans.

Nanomedicine is an emerging new field whose applications toward PDD are maturing. Despite the high expectations and all the encouraging and disappointing clinical outcomes, for example Pulmaquin (a liposome formulation of ciprofloxacine that was failed to be approved by the FDA for the inhalation treatment of non-CF bronchiectasis) or AeroLef (a liposomal formulation of fentanyl that failed Phase IIb clinical trials for the moderate or severe acute pain in postsurgical setting in adults), we are starting to see its promises to be realized on successful and revolutionary contributions such as Arikayce. Nanomedicines have all the potential to become an innovative class of therapeutics for PDD for either local or systemic delivery. To achieve this goal, fundamental research should continue to explore new nanomaterials and possibilities so as to improve the therapeutic efficacy and applicability of approved drugs, to improve the patient's compliance by reducing administration frequency, to reduce the toxicity and undesirable effects, and to gain insights into the nanotoxicological aspects of inhaled nanomedicines to ensure their safety.

REFERENCES

[1] F. Lavorini, F. Buttini, O.S. Usmani, 100 years of drug delivery to the lungs. Handb. Exp. Pharmacol. 260 (2019) 143–159, https://doi.org/10.1007/164_2019_335.

[2] S.W. Stein, C.G. Thiel, The history of therapeutic aerosols: a chronological review. J. Aerosol Med. Pulm. Drug Deliv. 30 (1) (2017) 20–41, https://doi.org/10.1089/jamp.2016.1297.