 Copyright CSC Publishing

BACK PAGE

Controlled release formulations for inhalation: Soon to appear?

David Cipolla
Aradigm Corporation

There are a number of controlled release technologies that have been used in marketed products; e.g., coated and composite tablets to delay or extend their oral release profile; transdermal patches and emulsion or suspension-based formulations for modified release topical applications; and injectable liposomes, microspheres, and implants to reduce administration frequency, improve compliance or provide sustained delivery. Compared to traditional pharmaceuticals, these controlled release products require additional formulation and analytical characterization to optimize drug release rates, distribution in the body and uptake by target cells. Paradoxically, even though there is a strong understanding of the mechanisms and limitations of the inhalation route relative to most other routes of administration, and many current inhaled therapies need to be taken several times a day, there are no approved controlled release inhalation products.[1,2] Why is this? When might this situation change?

Three constraints

Many of those aforementioned controlled release technologies have been evaluated via the pulmonary route in research studies over the past three decades,[2,3] but only the liposome formulation platform has resulted in products advancing into late stage clinical trials.[4] One barrier to the adoption of new technologies for pulmonary delivery is that many of the excipients in those technologies may have unknown safety in the respiratory tract. That means that expensive and lengthy preclinical inhalation safety studies would have to be conducted before pivotal clinical trials could be initiated. In contrast, liposomes have an advantage in that they can be manufactured using lipids, similar to or identical to those naturally present in the lung, thus imparting biocompatibility and reducing toxicity concerns.[4]

A second constraint is that rapid mucociliary clearance limits the residence time of deposited particles in the airways to hours, not days, thus placing an upper boundary on the potential benefit of a controlled release inhaled product.[1] Clearance mechanisms in the deep lung are slower, primarily driven by alveolar macrophage uptake. Thus, a reduction in the administration frequency from multiple times per day to once-daily may be practicable. However, carrier materials that may not be readily removed by macrophages or metabolic pathways would raise concerns about their long term accumulation in the lung.[2]

This leads to the last constraint: the opportunity space. The decision to develop a new inhaled product is only meaningful if its target product profile addresses an unmet medical need or it is likely to be superior to the competitive products in a significant way—e.g., improved efficacy, safety and compliance leading to tangible socioeconomic benefits. A more convenient administration profile is simply not enough. Most inhaled drugs for asthma and COPD are relatively inexpensive, and therefore, the likely higher cost associated with the modified release technology must provide justifiable upside for patients and payors. In spite of this, there is an opportunity to address other lung diseases for which there are inadequate alternatives; e.g., lung cancer and lung infections.[4,5]

Opportunities to treat lung diseases

In lung cancer, inhaled controlled release chemotherapeutic formulations have the potential to improve efficacy, due to higher sustained drug concentrations at the site of the tumors, while reducing systemic exposure to drug and the accompanying side effects.[5] While success has proven elusive, liposomal oncology formulations have shown promise in animal studies.[4] In contrast, there are signs of remarkable progress in the treatment of patients with lung infections for which there are no approved therapies. Pulmaquin, liposomal ciprofloxacin (Aradigm Corporation), delayed the time to first exacerbation in a Phase 2 trial in non-cystic fibrosis (CF) bronchiectasis patients colonized with *Pseudomonas aeruginosa* and a

Copyright CSC Publishing

Phase 3 trial has been initiated.[4] In a Phase 2 trial in patients with non-tuberculous mycobacteria, dosing of Arikace, liposomal amikacin (Insmed, Inc.), has been completed and results should be available in 2014. Therefore, the arrival of inhaled controlled release formulations may be imminent.

References

1. Patton, J.S., J.D. Brain, L.A. Davies, et al., The particle has landed—characterizing the fate of inhaled pharmaceuticals. J Aerosol Med Pulm Drug Deliv, 2010. 23 Suppl 2: p. S71-87.

2. Gonda, I., Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract. Crit Rev Ther Drug Carrier Syst, 1990. 6(4): p. 273-313.

3. Sakagami, M. and P.R. Byron, Respirable microspheres for inhalation: the potential of manipulating pulmonary disposition for improved therapeutic efficacy. Clin Pharmacokinet, 2005. 44(3): p. 263-277.

4. Cipolla, D., I. Gonda and H.-K. Chan, Liposomal formulations for inhalation. Therapeutic Delivery, 2013. 4(8): p. 1047-1072.

5. Cipolla, D., T. Redelmeier, S. Eastman, et al., Liposomes, niosomes and proniosomes—a critical update of their (commercial) development as inhaled products. Respiratory Drug Delivery Europe 2011, 2011. p. 41-54.

David Cipolla is Senior Director of Pharmaceutical Sciences, Aradigm Corporation, 3929 Point Eden Way, Hayward, CA, US, 94545, Tel: +1 510 265-9000, cipollad@aradigm.com. Website: www.aradigm.com.