European Journal of Pharmaceutical Sciences 205 (2025) 106988



Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps



Editorial

Editorial: Pulmonary drug delivery



1. Significance of the special issue

This Special Issue, entitled "*Pulmonary Drug Delivery*", compiles pioneering research and advancements in the field of respiratory drug delivery. Understanding the various factors influencing drug deposition, formulation design, device selection and bioequivalence assessment is crucial for developing effective, sustainable and safe inhaled therapies. Continued research in this area will lead to improved treatments for a wide range of respiratory and systemic diseases.

2. Overview of the published articles

Glieca et al. describe the development of a dry powder inhaler formulation of LCB1, an ACE2 decoy polypeptide that aims to neutralise SARS-CoV-2 in the lungs (Glieca et al., 2023). The researchers used spray drying with trehalose and l-leucine as excipients to produce LCB1 particles with an MMAD of 3.09 μm and FPF of 58.6 %. The significance of achieving peripheral lung deposition is highlighted, as it allows for localised neutralisation of the virus, potentially preventing its spread into the bloodstream and reducing the severity of lung damage.

Alhajj and colleagues focus on enhancing the pulmonary delivery of ciprofloxacin, an antibiotic, and quercetin, an antioxidant, by developing spray-dried formulations with improved dissolution and permeation properties (Alhajj et al. 2024). The study examines the impact of different mucoactive agents, such as mannitol, N-acetylcysteine, and ambroxol, on the physicochemical properties and aerosol performance of the formulations. The authors suggest that the optimised formulations may improve the treatment of *Pseudomonas aeruginosa* lung infections in cystic fibrosis patients.

Bahlool and co-workers describe the development of all trans retinoic acid (ATRA)-loaded PLGA nanoparticles using microfluidics for treating tuberculosis (Bahlool et al. 2024). The study demonstrates that these nanoparticles effectively inhibit *Mycobacterium tuberculosis* growth in alveolar epithelial cells *in vitro*. The researchers also evaluate the delivered dose of the nanoparticles using 3D-printed head models and simulating adult and paediatric breathing patterns. The authors propose that this inhalable ATRA formulation offers advantages over traditional oral administration for treating tuberculosis.

The article by Bender and colleagues focuses on the development and characterisation of curcumin-loaded tetraether lipid liposomes for pulmonary drug delivery and photodynamic therapy (Bender et al. 2024). The study demonstrates the stability of these liposomes during nebulisation using a vibrating mesh nebuliser. The authors assess the liposomes' biocompatibility and photodynamic efficacy in 2D and 3D cell culture models, as well as an *in ovo* model. The study suggests that these liposomes are a promising drug delivery system for targeted treatment of lung cancer.

Xia et al. investigated the pharmacokinetics of hydroxychloroquine in rat lungs after administration via different routes (oral, intratracheal, and nose-only inhalation) (Xia et al. 2024). The study compares the lung retention and systemic exposure of hydroxychloroquine delivered using various nebulisers and formulations (salt- and freebase-based). The authors highlight that understanding the spatiotemporal distribution of inhaled drugs in the lungs is crucial for optimising treatment efficacy and safety. Nose-only inhalation achieved higher and sustained lung concentrations compared to oral administration, demonstrating the potential of targeted pulmonary delivery.

The article by Gerde et al. explores a novel method for regional lung targeting using the PreciseInhale® system, which allows controlled delivery of aerosol boluses to specific lung regions using a breath-hold technique (Gerde et al. 2024). The study investigates the feasibility of this approach in healthy volunteers by administering a fluticasone/-salmeterol aerosol. Aerosol puffs were extracted from a medical inhaler then subsequent delivery to volunteers. The authors found that the system delivered consistent doses with low variability, highlighting its potential for studying regional drug disposition and effects in the lungs. Regional targeting influenced the systemic appearance of fluticasone propionate and salmeterol xinafoate differently.

Singh, in his publication, discusses the regulatory challenges and perspectives surrounding bioequivalence (BE) evaluation for orally inhaled drug products (OIDPs) (Singh 2024). The author highlights the limitations of traditional BE approaches based solely on systemic drug concentrations, particularly for locally acting drugs delivered via inhalation. The author advocates for alternative BE methods that consider local drug deposition and effects in the lungs to ensure therapeutic equivalence between generic and reference OIDPs. The article presents a comparative analysis of the BE requirements for OIDPs in the US and the EU, emphasising the differences in their approaches.

De Boer addresses the environmental impact of inhalers, specifically greenhouse gas emissions and plastic waste (de Boer 2024). The author discusses various strategies for reducing this burden, such as replacing metered-dose inhalers (MDIs) with dry powder inhalers (DPIs) and exploring the use of bio-based and biodegradable plastics for inhaler construction. The article also underscores the importance of considering potential consequences of any modifications to inhaler design or prescription practices, such as impacts on disease control and patient satisfaction.

https://doi.org/10.1016/j.ejps.2024.106988

Available online 11 December 2024
0928-0987/© 2024 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

3. Key concepts and insights

The eight articles collectively illustrate the complexity of pulmonary drug delivery and its impact on drug development and clinical practice. Key insights from these articles can be summarised as follows,

- **Targeted delivery to the lungs offers several advantages:** Direct delivery to the lungs can enhance efficacy, reduce systemic side effects, and provide rapid onset of action.
- **Formulation design is crucial for effective pulmonary delivery:** Developing stable and respirable formulations is essential for ensuring drug deposition in the target lung regions.
- **Choice of inhaler device impacts drug delivery:** Different inhaler devices deliver varying doses and particle size distributions, affecting drug deposition and therapeutic outcomes.
- **Regional lung targeting can optimise treatment:** Delivering drugs to specific lung regions can maximise therapeutic effects while minimising side effects.
- **Bioequivalence assessment for inhaled drugs requires careful consideration:** Traditional BE approaches may not be suitable for locally acting inhaled drugs, and alternative methods that assess local lung deposition and effects are necessary.
- **Environmental sustainability is an important factor in inhaler development:** Reducing greenhouse gas emissions and plastic waste associated with inhalers is crucial for minimising their environmental impact.

We acknowledge the use of NotebookLM (http://notebooklm.google.com) at the drafting stage of the writing process with the creation of article summaries for this editorial.

Data availability

No data was used for the content described in the article.

CRediT authorship contribution statement

Carsten Ehrhardt: Conceptualization, Writing – original draft, Writing – review & editing. **Francesca Buttini:** Writing – review & editing. **Imran Saleem:** Writing – review & editing. **Regina Scherließ:** Writing – review & editing. **Ayca Yıldız-Peköz:** Writing – review & editing.

Declaration of competing interest

None.

Acknowledgments

This work was supported by grants from the Society for Research Promotion Lower Austria (Gesellschaft für Forschungsförderung Niederösterreich, LS17–009, CE), Enterprise Ireland (IP/2020/0959, CE).

References

Alhajj, N., Yahya, M.F.Z.R., O'Reilly, N.J., Cathcart, H., 2024. Development and characterization of a spray-dried inhalable ternary combination for the treatment of Pseudomonas aeruginosa biofilm infection in cystic fibrosis. Eur. J. Pharm. Sci. 192, 106654. https://doi.org/10.1016/j.ejps.2023.106654.

Bahlool, A.Z., Cavanagh, B., Sullivan, A.O., MacLoughlin, R., Keane, J., Sullivan, M.P.O., Cryan, S.A., 2024. Microfluidics produced ATRA-loaded PLGA NPs reduced tuberculosis burden in alveolar epithelial cells and enabled high delivered dose under simulated human breathing pattern in 3D printed head models. Eur. J. Pharm. Sci. 196, 106734. https://doi.org/10.1016/j.ejps.2024.106734.

Bender, L., Preis, E., Engelhardt, K.H., Amin, M.U., Ayoub, A.M., Librizzi, D., Roschenko, V., Schulze, J., Yousefi, B.H., Schaefer, J., Bakowsky, U., 2024. *In vitro* and *in ovo* photodynamic efficacy of nebulized curcumin-loaded tetraether lipid liposomes prepared by DC as stable drug delivery system. Eur. J. Pharm. Sci. 196, 106748. https://doi.org/10.1016/j.ejps.2024.106748.

de Boer, A.H., 2024. The environmental burden of inhalation. Eur. J. Pharm. Sci. in press, 106893. https://doi.org/10.1016/j.ejps.2024.106893.

Gerde, P., Sjöberg, C.O., Bäckroos, H., Englund, J., Wangheim, M., Litorp, H., 2024. Regional lung targeting with a fluticasone/salmeterol aerosol using a bolus breath hold method of the PreciseInhale® system: a first evaluation in humans. Eur. J. Pharm. Sci. 196, 106742. https://doi.org/10.1016/j.ejps.2024.106742.

Glieca, S., Cavazzini, D., Levati, E., Garrapa, V., Bolchi, A., Franceschi, V., Odau, S., Ottonello, S., Donofrio, G., Füner, J., Sonvico, F., Bettini, R., Montanini, B., Buttini, F., 2023. A dry powder formulation for peripheral lung delivery and absorption of an anti-SARS-CoV-2 ACE2 decoy polypeptide. Eur. J. Pharm. Sci. 191, 106609. https://doi.org/10.1016/j.ejps.2023.106609.

Singh, G.J.P., 2024. Relevance of distinctions and parallels between the US and EU guidelines for determination of comparative effectiveness and safety of the orally inhaled drug products. Eur. J. Pharm. Sci. 201, 106872. https://doi.org/10.1016/j.ejps.2024.106872.

Xia, W., Kolli, A.R., Kuczaj, A.K., Szostak, J., Lam, S., Toh, W.W., Purwanti, A., Tan, W.T., Ng, R., Phillips, B., Peitsch, M.C., Hoeng, J., 2024. Aerosol delivery and spatiotemporal tissue distribution of hydroxychloroquine in rat lung. Eur. J. Pharm. Sci. 194, 106693. https://doi.org/10.1016/j.ejps.2024.106693.

Carsten Ehrhardt[a,*], Francesca Buttini[b], Imran Saleem[c], Regina Scherließ[d], Ayca Yıldız-Peköz[e]

[a] *School of Pharmacy and Pharmaceutical Sciences and Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, Ireland*

[b] *Food and Drug Department, University of Parma, 43124 Parma, Italy*

[c] *School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool L3 3AF, UK*

[d] *Department of Pharmaceutics and Biopharmaceutics, Kiel University, 24118 Kiel, Germany*

[e] *Department of Pharmaceutical Technology, Faculty of Pharmacy, Istanbul University, 34116 Istanbul, Türkiye*

[*] Corresponding author.
E-mail address: ehrhardc@tcd.ie (C. Ehrhardt).