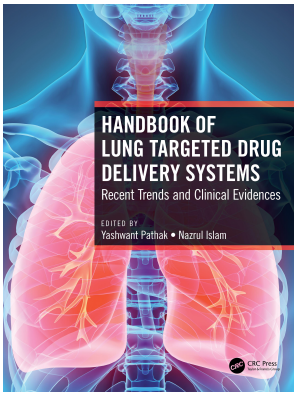

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

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In Vivo Animal Models for Lung Targeted Drug Delivery Systems

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In Vivo Animal Models for Lung Targeted Drug Delivery Systems

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10.1 Introduction

In the modern era of persisting chronic diseases, the efficacy of a treatment is highly reliant on the mode of transportation by which the drug is delivered with the most advantageous concentration of the drug (1). The gaps in this efficacy of the treatment of severe diseases has revealed a pressing need for a multidisciplinary approach for drug delivery to the target organ (1). Lung targeted drug delivery systems have become of tremendous scientific interest in the field of research because the organ is capable of absorbing pharmaceutical drugs either for local deposition or for systemic delivery. There have been several studies considering different drug delivery systems using newer mathematical models. The use of computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK) modeling are some of the newer concepts that have shown excellent in vivo results and several other modeling techniques are showing promising results (2). There are studies focusing on each and every aspect of the drug delivery systems while using newer techniques such as using aerosolized drug forms rather than the conventional oral forms which in turn increase patient compliance, encourage ideal drug dosage, and decrease toxicity.

10.2 Coupled In Silico Platform: Computational Fluid Dynamics (CFD) and Physiologically Based Pharmacokinetic (PBPK) Modeling

There are a number of factors that influence the formulation of inhaled drugs, these factors such as quality of the drug, efficacy of the drug, and physiological parameters in the population make it challenging to get a final product(2). To overcome such challenges, in silico predictive tools can be used to facilitate design of inhaled pharmaceutics. The complexity of physiological processes and interactions within it can be studied through computational models and advanced simulation tools which can further facilitate the development of inhalation medicines (2). Technological advancements, like cheaper computer power and ease in availability of powerful software, have led to an increase in the use of computer-based simulations (3). CFD is used in determining airflow patterns and turbulence levels for a device design and also to provide an accurate simulation of the particles and droplets by subjecting them to several forces, turbulence, and wall interactions (3). Particle interaction cannot be considered when using the CFD technique which is the main disadvantage (4). There are several other models available, like the discrete phase model (DPM), two-fluid model, mixture model, dense dispersed phase model (DDPM), and the discrete element method (DEM) (5). Dry powder inhalers (DPIs) are used to deliver drugs in a dry powder form without the need of a propellant. This form of drug delivery produces aerosol particles that might be advantageous to deliver the drug faster to the lungs (6). The only disadvantage is that the efficiency is less, so <30% of the dose reaches the lungs (7). The major factor affecting the deposition profile of DPIs are patient-related factors and physical properties of dry powder formulations (8). A study by Zhou et al. (9) in 2013 researched the device design and its effect on commercially used DPIs and other kinds of commercially available products. A study by Jiang et al. (10) in 2012 researched using a similar method investigated the effect of powder residence time on the performance of the Aerolizer DPI. There have been several other studies that have focused on different aspects of the DPIs and their interactions with human lungs. Computer-based analysis provided information that can help us understand dispersion mechanisms of different drug delivery models better. This knowledge can further be helpful in enhancing inhaler design in order to create more efficient drug delivery device (2).

10.3 Modeling and Simulation of Biopharmaceutical Performance in Lung Drug Delivery

Biopharmaceutical modeling has gained much popularity in the field of pharmacology. *Biopharmaceutical performance* refers

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to the influence of pharmaceutical formulation variables on in vivo performance (11). A 2019 study by Sou et al. researched antibiotic resistance of *Pseudomonas aeruginosa* (PA) lung infections using quorum sensing inhibitors (QSIs) that are meant for inhibiting biofilm formation and sensitize PA to antibiotic treatments. For such respiratory conditions, it is essential to have targeted lung drug delivery systems available for which proper models need to be developed. This study has demonstrated that pharmacometrics modeling can be an essential tool to facilitate drug selection, maintain drug dosage, and develop future development of the treatment (12,13). This kind of developed model can also be used in association with an infection model for studying drug exposure-response relationships to improve the understanding of the pharmacokinetic–pharmacodynamic relationships of QSIs (12). Thus, this is an important concept to understand and there is a need for development of bio-models that can facilitate pulmonary drug absorption while maintaining patient safety.

10.4 Clinically Relevant Test Methods to Establish In Vitro Equivalence for Spacers and Valved Holding Chambers Used with Pressurized Metered Dose Inhalers (pMDIs)

Bioequivalence (BE) is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in a pharmaceutical equivalent becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (Code of Federal Regulations Title 21, 320.1). Spacers (S) and valved holding chambers (VHCs) are pressurized metered-dose inhaler (pMDI) accessory devices, designed to overcome commonly faced problems by patients when administering aerosol via a pMDI. The development of spacers/VHCs (S/VHC) was in response to the frequently encountered patient-related issues with pMDI techniques involving poor coordination between actuation and inhalation, and local side effects arising from oropharyngeal deposition (14,15). Moreover, S/VHCs substantially modify the aerodynamic particle size distribution (APSD) of the inhaled medication, and potentially the spatial distribution of the mass of active pharmaceutical ingredient(s) [API(s)] depositing in the respiratory tract (16). Clinically relevant in vitro BE testing is not yet much emphasized by the standard authorities, however future consideration of such testings would help better understand the clinical outcomes, performance predictions, similarities, and differences between reference and test products (16). Currently, a three-part strategy is proposed whereby in vitro testing for BE can simulate more clinically relevant conditions than in the current compendial procedures: (i) The inclusion of a short delay between inhaler actuation and sampling onset is appropriate when determining APSD at flow rate(s) suitable for the intended patient population. (ii) Assessment of total emitted mass ex S/VHC by simulating tidal breathing pattern(s) appropriate for intended use. (iii) Incorporation of appropriate face model(s), representative of the intended patient age range(s), into test procedures for S/VHCs with facemasks, enabling clinically appropriate dead space and fit-to-face to be simulated (16).

10.5 Lipid Nanoparticles' Biocompatibility and Cellular Uptake in a 3D Human Lung Model

In the last couple of decades, researchers have explored the use of nanoparticle-based drug delivery systems to carry, protect, and to deliver drugs directly to the site of infection, leading to reduction in the amount and frequency of dosage of the drug and thereby preventing the toxicities related to the therapy while improving patient compliance (17). The physical and chemical properties of nanoparticles (NP), including particle size, surface, and morphology, are determinant factors that influence their transport and deposition within the respiratory tract (18,19). After inhalation, the NPs are usually deposited in the alveolar region of the lungs (20). Having a large epithelial surface of 150 m^2, the respiratory tract has a dense network of immune cells consisting of macrophages and dendritic cells (DC) (21). These cells play a crucial role as a protective barrier for the inhaled drug particles (22). Other factors contributing to the deposition of drug particles include the type of device for drug delivery and the magnetic field (23).

Nanostructured lipid carriers (NLC) are another alternative that can be used as a lung drug delivery system because of their biocompatibility, high drug loading capacity, modifications to size and morphology, target specificity, and stability (20). The disadvantages for NLC are their potential toxicity and biodistribution in lungs (20). The study by Magalhaes et al., focuses on studying these potential toxicities on monocultures and 2D co-cultures. This study focused on testing on 3D lung models, developing non-mannosylated NLCs and mannosylated NCLS (M-NLC) where they were characterized on the basis of size, morphology, polydispersity (PDI), and zeta (ζ)-potential. Their cellular uptake was labelled using a fluorophore and these NLCs were submerged or used through a pseudo air–liquid interface (ALI) approach in vivo. A post 24-hour exposure check was performed to assess the biocompatibility and targeting efficiency of NLCs and M-NLCs using techniques like cell viability, pro-inflammatory assays, and visualization of the lung tissue with confocal laser scanning microscopy. The applications for nano-based systems for lung drug delivery have been extensively researched to improve the treatment and drug delivery for infectious diseases targeting the lungs (20). The study by Magalhaes et al., has proven that exposure to all the tested NLCs formulations does not affect or alter the cell membrane integrity and cellular morphology in the lungs, nor do they elicit any cytotoxic or pro-inflammatory responses after the 24-hour exposure window. These drug delivery systems can thus be good candidates for lung drug delivery.

10.6 Designing In Vitro Bioequivalence Studies for Pressurized Metered Dose Inhalers with Spacer or Valved Holding Chamber Add-On Devices

Bioequivalence (BE) is defined as the absence of a significant difference in the rate and extent to which the active ingredient

or active moiety in a pharmaceutical equivalent becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (Code of Federal Regulations Title 21, 320.1). A study by Sandell and Mitchell (24) researched the analytical test methods and associated statistical considerations by considering the laboratory testing of pressurized metered dose inhaler–spacer/valved holding chamber (pMDI-S/VHC) combinations for in vitro bioequivalence (IVBE) and concluded that, for these add-on devices, information provided in developing correlations were in support of IVBE. The methods used for this study were presented using four different scenarios for comparing TEST ("second entry" or "generic") versus REF ("innovator"): (i) innovator and second entry product pMDI alone without any S/VHC (baseline comparison); (ii) innovator and second entry pMDI product with the same S/VHC; (iii) innovator pMDI product with existing S/VHC and second entry product with a different S/VHC; and (iv) introduction of a second, different S/VHC to be used with a given innovator pMDI product (24). The important aspects to be considered include delayed inhalation, utilizing age-appropriate flow rates, and using anatomically appropriate face models for evaluation of devices with a facemask (24). The results showed that a proper statistical design of experiment was provided for each scenario, while also using alternative approaches for calculation of confidence intervals for the mean of TEST/REF relationship. It was thus concluded that precise calculations can be obtained using different statistical approaches (24).

10.7 International Guidelines for Bioequivalence of Locally Acting Orally Inhaled Drug Products: Similarities and Differences

Bioequivalence (BE) is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in a pharmaceutical equivalent becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (Code of Federal Regulations Title 21, 320.1). BE is vital to infer therapeutic equivalence (TE) between the generic and corresponding reference drug product in the abbreviated new drug applications (ANDAs). It also supports the formulation modifications during the new drug product development phase, as well as for post-approval changes in drug applications (25). Currently, to determine BE for systemically acting drug products, several regions make use of pharmacokinetic studies (26). These drugs reach their action sites through systemic circulation. However, such an approach of locally acting drugs may not be enough in all cases to establish BE since their intended actions and deliveries do not rely on systemic circulation. Therefore, this presents a need for an alternative approach for BE of locally acting drugs (25). Orally inhaled drug products (OIDPs) includes products such as the dry powder inhaler (DPI), metered-dose inhaler (MDI), and nebulization products. Most inhalation products are designed to act as a local agent for the lungs, and their drug delivery does not necessarily rely on systemic circulation (25). Another challenge is to find a biomarker that is sensitive enough to clinically detect the potential differences in local drug delivery. Thus, establishment of proper BE standards for locally acting OIDPs has been an ongoing challenge for regulatory agencies across the globe (25). Currently, only limited international jurisdictions have regulatory guidelines on BE standards with varying recommended BE standards; details are available in Table 10.1 (25).

10.8 In Vitro Evaluation of Aerosol Delivery by Different Nebulization Modes in Pediatric and Adult Mechanical Ventilators

A nebulizer is a small machine that is used to convert liquid medicine into aerosolized form. These aerosolized forms of medications are mainly used to treat mechanically ventilated patients for the administration of bronchodilators (36). A study conducted by Wan et al., 2014 in (36) studied the delivery of aerosolized drug administered through three modes of nebulization for mechanical ventilation considering the influence of the type of aerosol generator, pattern of nebulization, and a patient's breathing pattern. This study also compared the efficiency of pneumatic nebulization modes provided by a ventilator using the pediatric and adult in vitro lung models. The results of the study showed that the percentage of total dose in both lung models was 5.1–7.5%, without any statistical significance among the three modes. Median nebulization times for inspiratory intermittent [IIM], continuous [CM], and expiratory intermittent [EIM] were 38.9, 14.3, and 17.7 minutes, respectively, and nebulization time for the three modes significantly differed ($P < 0.001$). The inhaled drug mass for the three nebulization modes with the adult lung model was similar to that of the pediatric lung model (7.39 ± 0.76 vs $6.27 \pm 0.69\%$, $P = 0.77$). The conclusion of the study was that aerosol drug delivery with a jet nebulizer placed proximal to the ventilator was not dependent on nebulization mode during simulated adult or the pediatric conventional mechanical ventilation, and that the use of EIM and CM modes of nebulization should be considered to decrease the treatment time (36).

Another study by Ke et al., 2020 in (37) studied soft mist inhalers that can generate aerosols with a smaller particle size as compared to the pressurized metered-dose inhalers. This study aimed to measure the particle size distribution of the soft mist inhalers when they are coupled with an inhalation aid, as well as to measure the efficacy of the delivery system in different actuation timings and circuit positions during mechanical ventilation with a pressurized metered-dose inhaler used as a suitable comparison. The results concluded that soft mist inhalers generated a smaller mass medium aerodynamic diameter than the pressurized metered-dose inhalers. During mechanical ventilation, the optimum way to deliver the both the inhalations was at 15 cm from the Y-piece and actuated at the end of expiration and the onset of inspiration, respectively. The conclusions from the study were that soft mist inhalers, when used with an inhalation aid, showed marginal improvement on the particle size distribution. Other factors that played an important role were the inhaler type, actuation timing, and position within the circuit (37).

TABLE 10.1

Similarities and Differences in the BE Guidelines for Orally Inhaled Drugs from Four Organizations: Australia – Therapeutic Goods Administration (TGA), Canada – Health Canada (HC), European Union (EU) – European Medicines Association (EMA), and the United States of America – Food and Drug Administration (FDA), with the Focus on the OIDPs Intended for Local Sites for Action

International Regulatory Authority	Agency	BE Guidelines Referenced	Scope	Date Posted/ Effective
Australia	Therapeutic Goods Administration	Guidance 19: Inhalation and nasal medicines/19.2 Generic MDI (27,28)	Support applications to register new inhalation and nasal medicine; applications to register generic inhalation and nasal medicines; requests to vary registered inhalation and nasal medicines. Include medicines for treating asthma; chronic obstructive pulmonary disease (COPD), other conditions of the lungs	August 9, 2013
Canada	Health Canada	Release of the Draft Guidance Document Data Requirements for Safety and Effectiveness of Subsequent Market Entry Inhaled Corticosteroid Products for Use in the Treatment of Asthma for Industry (26)	Support Abbreviated New Drug Submissions (ANDS); Supplemental New Drug Submissions (SNDS). Include medicines for: corticosteroid for asthma treatment (not COPD)	September 19, 2011
Canada	Health Canada	Guidance to Establish Equivalence or Relative Potency of Safety and Efficacy of a Second Entry Short-Acting Beta2-Agonist Metered-Dose Inhaler (29)	Short-acting beta-2 agonist metered-dose inhaler only	February 1, 1999
Canada	Health Canada	Guidance for Industry Pharmaceutical Quality of Inhalation and Nasal Products (section Regional information) (30)	Addresses quality aspects of new marketing authorization applications (including for generic products) and does not outline expected quality aspects related to changes in existing inhalation and nasal productsIncludes products for administration of the drug substance to the lungs, such as pressurized MDI, DPI, products for nebulization, and non-pressurized MDIs, as well as pressurized metered-dose nasal sprays, nasal powders, and nasal liquids	October 1, 2006
European Union	European Medicines Agency	Doc. Ref. CPMP/EWP/4151/00 Rev. 1: Guideline on The Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma And Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in Children and Adolescents(31,32)	Recommendations for demonstration of therapeutic equivalence between two inhaled products, in the context of abridged applications or variations/ extensions to a marketing authorization, used in the management and treatment of adult patients with asthma and/or COPD and children and adolescents with asthma. Include dosage forms: pressurized MDI; breath-operated MDI; pressurized MDI with spacers or holding chambers; non-pressurized MDI; solution and suspensions for nebulization; DPIs	January 22, 2009
United States of America	Food and Drug Administration	Draft Bioequivalence Recommendations for Specific Product: Fluticasone Propionate/ Salmeterol Xinafoate Dry Powder Inhaler (FP-SX DPI) (33,34)	For FP-SX DPI	September 2013
United States of America	Food and Drug Administration	Draft Bioequivalence Recommendations for Specific Product: Nebulized Budesonide Inhalation Suspension (35)	For nebulized budesonide inhalation suspension	September 2012
United States of America	Food and Drug Administration	Draft Bioequivalence Recommendations for Specific Product: Albuterol Sulfate Metered-Dose Inhaler (33)	For albuterol sulfate MDI	June 2013

10.9 Conclusion

Pulmonary drug delivery is a complex process with potentially promising future prospects to serve a number of considerations for physical and biological merits and demerits. With supportive lung physiological parameters and favorable *ex vivo* models study outcomes, lung drug delivery could potentially outweigh the conventional drug delivery, having its own limitations of high dosing frequency, toxicity, and low efficacy. In the last 20 years, CFD models have been exceptional and made significant progress in understanding the physics behind pulmonary drug delivery (38). Newer mathematical models have made it easier to compute and find effective drug delivery systems while considering vital factors such as minimizing dosage and time, individual lung profile, and patient compliance and safety (38). The applications for nano-based systems (NP, NLC, M-NLC) for lung drug delivery have been extensively researched using 3D lung models to improve the treatment and drug delivery targeting the lungs (20). Availability of limited information on BE regarding orally inhaled drugs results in a few international jurisdictions having regulatory guidelines on BE standards, with varying recommendations also a potential problem. A study by Fok et al. 1996 and Goralski and Davis (39) addresses challenges with pediatric aerosol drug delivery and issues with current drug delivery systems. There have been several in vivo study models which have shown promising results in theory but there needs to be more research in to accurately design models that will work efficiently for lung drug delivery.

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