Journal of Drug Delivery Science and Technology 37 (2017) 81–87

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Adapting the ICRP model to predict regional deposition of the pharmaceutical aerosols inhaled through DPIs and nebulizers

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ARTICLE INFO

Article history:
Received 26 August 2016
Received in revised form
30 November 2016
Accepted 8 December 2016
Available online 10 December 2016

Keywords:
Drug delivery
Dry powder inhalers
ICRP
Lung
Nebulizer

ABSTRACT

Using inhaler devices, drug delivery to the lung has been practiced for a long time to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). The key question in this practice is how to deliver the drug to the regions of interest efficiently. Significant efforts have been made to develop models of depositional behavior of inhaled particles. The semi-experimental International Commission on Radiological Protection (ICRP) model is frequently used to predict depositional behavior of inhaled particles. Here, we have tried to adapt this model for predicting deposition of pharmaceutical particles that are inhaled through dry powder inhalers (DPIs) and nebulizers. We attempted to use a more proper extrathoracic deposition formula accounting for breath holding and bolus timing (in case of DPIs) and possible evaporation of droplets (in case of nebulizers). Two computer programs for DPIs and nebulizers were developed which can be freely accessed through e-mail contact to the first author.

1. Introduction

In the context of drug delivery to the lung, it is crucial to know the fraction of the drug that each region in the lung receives. This fraction depends on many parameters including diameter and density of the drug particles and flow rate of the inhalation, tidal volume. It is thus necessary to provide a model that can take into account input parameters and conditions, and predict the resulting regional deposition. Such a model can help finding optimum parameters in designing drugs, inhalers and treatment process.

Extensive effort has been made to identify correlations relating regional depositions to the parameters that characterize the inhaled aerosols [1]. These efforts have formed the basis of semi-empirical models, among which the ICRP (International commission on radiological protection) model (developed in 1994) [2,3] is probably the most frequently employed one, which continues to be used in the recent years [4,5]. It should, however, be mentioned that as discussed by Finlay and Martin [6], experimental measurements do not provide detailed and robust regional deposition data; therefore, it appears that no existing model, including this one, benefits from a robust verification.

Although the ICRP model was originally developed to predict hazardous deposition of airborne nuclear-related particles, it was later used for pharmaceutical applications as well [7]. The condition through which drug particles are inhaled is usually different from that of normal breathing on which the model is based. In case of DPIs, a usually small mouthpiece combined with a usually high flow rate produces an aerosol jet that shows a different depositional behavior in the extrathoracic region. In addition, to enhance desirable deposition from DPIs, there are two techniques of breath holding and bolus timing (tuning the time of the drug release), which are not included in the model. In case of droplets, using nebulizers, a considerable evaporation can change the size of droplets and affect the whole deposition pattern, which is not accounted for in the model. These issues make the original form of the model insufficient for pharmaceutical applications.

Here, we tried to adapt the ICRP model to address the above-mentioned pitfalls to develop a tool for better estimation of the

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http://dx.doi.org/10.1016/j.jddst.2016.12.002
1773-2247/

deposition of pharmaceutical particles inhaled through DPIs and nebulizers.

2. Method and formulation

As mentioned, the method is based on the ICRP model, which is not re-written here for the sake of brevity. ICRP model is a semi-empirical model that was developed in 1994 for modeling the behavior of particles in the lungs. Briefly, ICRP model estimates the clearance half times from different compartments of respiratory tract, and also estimates the fractions of particles cleared from each compartment [2,3]. In the following sections, we will only address the changes that have been made in the model.

2.1. DPI

2.1.1. Extrathoracic deposition

To account for the inhalation condition of DPIs, extrathoracic filter of the ICRP model has been replaced with the specific formulae provided by DeHaan and Finlay [8] for mouth and laryngeal depositions. For extrathoracic deposition during exhalation, the ICRP filter was retained.

2.1.2. Breath holding

Patients using DPIs are usually advised to hold their breath for seconds after inhalation and before exhalation. This provides more time for particles to deposit through the mechanisms of sedimentation and diffusion, both of which are directly proportional to time.

In the ICRP model, deposition efficiency results from the combination of thermodynamic (η_{th}) and aerodynamic (η_{ae}) efficiencies through as shown by the equation $\eta = \sqrt{\eta_{th}^2 + \eta_{ae}^2}$, the former accounting for diffusion and the latter for impaction and sedimentation. In the alveolar region, it is known that impaction has a negligible role, thus only mechanisms of diffusion and sedimentation act during all phases of inhalation, breath holding and exhalation. In case of alveolar region, we simply added the time of breath holding to the normal transient time. In bronchial and bronchiolar regions, the thermodynamic efficiency was calculated similar to the inhalation phase with t_{bh} instead of the transient time. However, the aerodynamic efficiency, which should no longer account for impaction, is calculated through the following equation

$$\eta_{ae} = \min\left(\frac{V_s \times t_{bh}}{d_{ch}}, 1\right) \tag{1}$$

where d_{ch} is a characteristic diameter being 5 and 2 ml in bronchial and bronchiolar regions, respectively. V_s is the settling velocity that is calculated as

$$V_s = \frac{\rho d^2 C_c g}{18\mu} \tag{2}$$

where the parameters are as follow: ρ particle density; d particle diameter; C_c Cunningham correction factor; g gravity; μ air viscosity.

Extrathoracic deposition through the breath holding period has been assumed with an efficiency of one; meaning that all trapped particles in the mouth are deposited. This has been assumed due to natural tendency of moving the tongue toward the palate during breath holding.

2.1.3. Bolus timing

It is naturally assumed in the ICRP model that particles' concentration is uniform during the inhalation time. If, however, one can tune the time and volume of drug release, there is opportunity for more efficient and targeted deposition. This feature has been added to the model, with care in calculating the transient times differently for deposition efficiencies and hygroscopic growth and also in calculating the fraction of the drug that passes or stays in each region during inhalation and breath holding. Bolus timing is described in the program by two variables of V_{b_bolus} and V_{bolus}; the first determines the inhaled volume before the release of the drug and the second determines the volume through which drug is released. Obviously, the sum of the two parameters should not exceed the tidal volume.

2.2. Nebulizer

Depending on the nebulizer type, the nebulizer stream might be mixed with a stream from the ambient air [9], which can lead to a considerable evaporation of the droplets, provided that the ambient air is not saturated with vapor. This idea has been used as a technique to adjust the size of the particles for more efficient deposition [10]. Finlay and Stapleton [11] developed a model to account for the evaporation of the droplets and emphasized the importance of two-way coupling between the droplets and the surrounding air. Their model addresses the evaporation dynamic from the point of mixing to all points through the lung. Here, we have employed a similar model; however, only up to the point that the stream enters the lung. Size changes through the lung have been followed using the equation provided in the ICRP model from the work by Ferron et al. [12].

To predict diameters of particles prior to entering the lung, four states have been defined that are shown in Fig. 1. In the following, we briefly explain the formulae used to find particles diameter at state 4.

Adiabatic saturation is assumed in the process of droplets formation (1–2). The balance of energy is written as

$$h_{a1} + \omega_1 h_{v1} + (\omega_2 - \omega_1) h_{l2} = h_{a2} + \omega_2 h_{v2} \tag{3}$$

where h and ω stand for enthalpy and humidity ratio, and the subscripts a and v refer to air and vapor, respectively. Humidity ratio is related to ambient pressure (p) and vapor pressure (p_v) as

$$\omega = 0.622 \frac{p_v}{p - p_v}, \tag{4}$$

and relative humidity is defined as

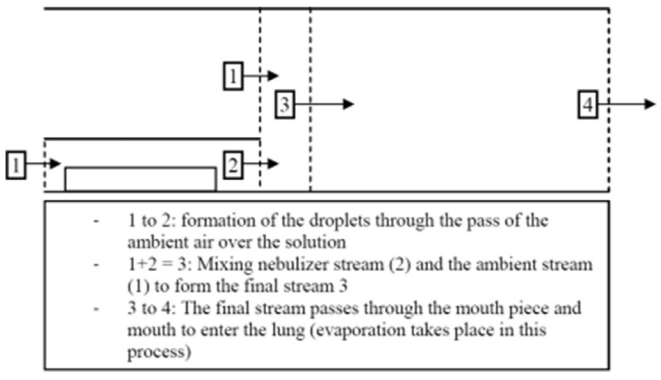

Fig. 1. Schematic of the processes before the aerosol enters the lung in nebulizers.