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Subject-variability effects on micron particle deposition in human nasal cavities

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ABSTRACT

Validated computer simulations of the airflow and particle dynamics in human nasal cavities are important for local, segmental and total deposition predictions of both inhaled toxic and therapeutic particles. Considering three, quite different subject-specific nasal airway configurations, micron-particle transport and deposition for low-to-medium flow rates have been analyzed. Of special interest was the olfactory region from which deposited drugs could readily migrate to the central nervous system for effective treatment. A secondary objective was the development of a new dimensionless group with which total particle deposition efficiency curves are very similar for all airway models, i.e., greatly reducing the impact of intersubject variability. Assuming dilute particle suspensions with inhalation flow rates ranging from 7.5 to 20 L/min, the airflow and particle-trajectory equations were solved in parallel with the in-house, multi-purpose Alya program at the Barcelona Supercomputing Center. The geometrically complex nasal airways generated intriguing airflow fields where the three subject models exhibit among them both similar as well as diverse flow structures and wall shear stress distributions, all related to the coupled particle transport and deposition. Nevertheless, with the new Stokes-Reynolds-number group, $Stk^{1.23}Re^{1.28}$, the total deposition-efficiency curves for all three subjects and flow rates almost collapsed to a single function. However, local particle deposition efficiencies differed significantly for the three subjects when using particle diameters $d_p = 2$, 10, and 20 μm. Only one of the three subject-specific olfactory regions received, at relatively high values of the inertial parameter $d_p^2 Q$, some inhaled microspheres. Clearly, for drug delivery to the brain via the olfactory region, a new method of directional inhalation of nanoparticles would have to be implemented.

1. Introduction

The pulmonary route for direct drug-aerosol delivery is an attractive approach to combat brain or lung diseases or to reach systemic regions. Of great potential is optimal targeting of solid tumors or severely inflamed areas with multifunctional particles promising lower side-effects and costs than other treatment options, such as chemotherapy or radiation (Kleinstreuer, Feng, & Childress, 2014; Kolanjiyil & Kleinstreuer, 2016; Kolanjiyil, Kleinstreuer, & Sadikot, 2016). For example, intranasal direct drug delivery is being considered as a possible and effective route to deliver vaccines, insulin, and medication for treating various

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diseases and disorders affecting the central nervous system (Illum, 2000; Illum, Tsuda, & Gehr, 2015; Mistry, Stolnik, & Illum, 2009). In case of intranasal drug delivery, it is quite challenging for the inhaled drugs to reach the olfactory region with the possibility of crossing the blood-brain barrier in order to reduce/eliminate brain tumors or to maximize the impact on the central nervous system (Dhuria, Hanson, & Frey, 2010; Thorne, Emory, Ala, & Frey, 1995). Even though intranasal delivery provides greater advantages, the drug-amount actually reaching the brain is quite low, but possibly higher than intravenous administration (Garcia, Schroeter, & Kimbell, 2015; Schroeter, Kimbell, & Asgharian, 2006; Thorne et al., 1995; Thorne, Pronk, Padmanabhan, & Frey, 2004). Clearly, intranasal *targeted* drug delivery to a specific location could improve delivery efficiency (Inthavong, Tian, Tu, Yang, & Xue, 2008; Shi, 2007; Shi, Kleinstreuer, & Zhang, 2008, 2007). In general, high particle deposition at any predetermined site depends largely on the given airway geometry as well as the fluid-particle inlet conditions, including the breathing mode and the type of inhaler employed (Keeler, Patki, Woodard, & Frank-Ito, 2016; Schroeter et al., 2006; Segal, Kepler, & Kimbell, 2008). The complex geometrical structure of the nasal cavity makes it difficult to predict the airflow and aerosol transport (Schroeter, Garcia, & Kimbell, 2010). Additionally, the geometrical variability among individuals raises significant challenges in developing efficient drug delivery devices (Garcia, Tewksbury, Wong, & Kimbell, 2009; Inthavong et al., 2008; Kimbell et al., 2007; Leong, Chen, Lee, & Wang, 2010).

Deposition of inhaled aerosols in human nasal cavity has been extensively studied using in vivo (Bennett & Zeman, 2005; K.-H. Cheng et al., 1996; Y. S. Cheng et al., 1996; Cheng, Yeh, & Swift, 1991; Kesavan, Bascom, Laube, & Swift, 2000; Kesavanathan & Swift, 1998; Kesavanathan, Bascom, Laube, & Swift, 1998; Rasmussen, Andersen, & Pedersen, 2000; Wiesmiller et al., 2003) in vitro (Cheng et al., 2001; Cheng, 2003; Cheng, Cheng, Yeh, & Swift, 1995; Garcia, Tewksbury, Wong, & Kimbell, 2009; L. Golshahi, M. L. Noga, R. B. Thompson, & W. H. Finlay, 2011; Kelly, Asgharian, Kimbell, & Wong, 2004a, 2004b; Schroeter, Tewksbury, Wong, & Kimbell, 2015a; Storey-Bishoff, Noga, & Finlay, 2008; Zwartz & Guilmette, 2001) and in silico (Corley et al., 2015; Dastan, Abouali, & Ahmadi, 2014; Garcia et al., 2015; Inthavong et al., 2006; Inthavong, Wen, Tian, & Tu, 2008; Kimbell et al., 2007; Liu, Matida, & Johnson, 2010; Schroeter et al., 2006, 2010; Schroeter, Garcia, & Kimbell, 2011; Shanley, Zamankhan, Ahmadi, Hopke, & Cheng, 2008; Shi et al., 2008; Shi, 2007; Shi, Kleinstreuer, & Zhang, 2007; Wang, Hopke, Ahmadi, Cheng, & Baron, 2008; Xi & Longest, 2008; Xi, Kim, Si, Corley, & Zhou, 2016; Zhang & Kleinstreuer, 2011) methods. The deposition results from these studies indicate that there exist significant variations in human nasal aerosol deposition. While the major reason for these variations is due to anatomical variations, differences in experimental techniques can also affect reported nasal aerosol deposition outcome (Kelly et al., 2004a, 2004b; Schroeter, Garcia, & Kimbell, 2011; Shi et al., 2007). Even though an in vivo deposition measurement on human subjects is the most physiologically realistic method, there are many limitations. Such experiments are restricted due to the usage of aerosols which may lead to side effects, especially when using radioactive aerosols, and hence are limited in the number of trials. Additionally, in vivo measurements cannot clearly provide detailed regional deposition measurements and the presence of subject variability limits comparative analyses without geometrical correlations (Y. S. Cheng et al., 1996; Rasmussen et al., 2000). Even though these limitations can be overcome with in vitro experiments, even small differences in the in vitro model geometry can significantly alter aerosol deposition. Recent investigations have shown that surface irregularities (surface roughness vs. surface smoothness) due to the differences in the fabrication process and/or due to the low resolution of the scanned images have resulted in significant variations in aerosol deposition (Dastan et al., 2014; Kelly et al., 2004a, 2004b; Schroeter et al., 2011; Shi et al., 2007). Hence, as an alternative to these experimental techniques numerical analysis, using Computational Fluid-Particle Dynamics (CF-PD), has shown many advantages including repeatability and regional deposition resolution (Kolanjiyil & Kleinstreuer, 2016, 2013). Recent developments in Magnetic Resonance Imaging (MRI) and Computer Tomography (CT) techniques have helped in reconstructing physiologically realistic models. Such subject-specific geometries can be coupled with the advancements in CF-PD simulation computer hardware and software technology to obtain detailed, accurate and realistic visualization of the flow field and particle transport/deposition (Kleinstreuer et al., 2014). For example, for direct drug delivery numerical analysis concerning nasal airway models has been able to reveal detailed nasal airflow fields (Garcia, Bailie, Martins, & Kimbell, 2007; Kim, Na, Kim, & Chung, 2013; Kimbell, Frank, Laud, Garcia, & Rhee, 2013), particle dynamics (Dastan et al., 2014; Garcia et al., 2015; Inthavong et al., 2006, 2008; Kimbell et al., 2007; Liu et al., 2010; Schroeter et al., 2006; Shanley et al., 2008; Shi et al., 2007, 2008; Shi, 2007; Wang et al., 2008; Xi & Longest, 2008; Xi et al., 2016; Zhang & Kleinstreuer, 2011), dosimetry of inhaled vapours (Asgharian, Price, Schroeter, Kimbell, & Singal, 2012; Morris, HAssETT, & Blanchard, 1993; Schroeter et al., 2008), and odourant delivery (Keyhani, Scherer, & Mozell, 1997). It can also assist in nasal surgery (Garcia et al., 2007; Kimbell et al., 2013; Rhee, Pawar, Garcia, & Kimbell, 2011), intranasal drug delivery and development of nasal drug delivery devices (Inthavong et al., 2006; Inthavong, Tian, Tu, Yang, & Xue, 2008b; Keeler et al., 2016; Kimbell et al., 2007).

As indicated, the results from nasal deposition studies have shown that the nasal aerosol deposition is a function of inhalation conditions and particle properties, including size, shape and density (Schroeter, Tewksbury, Wong, & Kimbell, 2015b; Shi et al., 2007). These studies suggest that the nasal passage acts as a filtering mechanism for the incoming particles which leads to large deposition in the anterior part, thereby reducing drug aerosols from reaching their predetermined areas (Garcia & Tewksbury, 2009; Liu et al., 2010). In the inertial regime (for particle diameters $\geq 1\mu m$) the aerosol deposition increases with the particle size and air flow rate, following a sigmoidal curve with very low deposition for lower micron particles (Shi et al., 2007a). For nanoparticles ($1 - 100\, nm$), aerosol deposition decreases with diameter due to higher diffusivity of smaller particles leading to higher nasal deposition (Garcia et al., 2015; Shi et al., 2008a). Even though nasal deposition has been investigated for different inhalation conditions and particle sizes, only a limited number of studies have focused on estimating the regional distribution of the deposited particles (Dastan et al., 2014; Garcia et al., 2015; Schroeter et al., 2006; Shanley, Zamankhan, Ahmadi, Hopke, & Cheng, 2008; Shi et al., 2007a; Zwartz & Guilmette, 2001) and it is still unknown how the regional distribution depends on subject variability. Subject variability in nasal deposition hinders development of intranasal therapeutic drugs, because variability in deposition leads to variability in drug dose and its reaction (Garcia, Tewksbury, et al., 2009).