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Journal of Drug Design and Research

Research Article

Effects of Three Dry Powder Inhalers on Deposition of Aerosolized Medicine in the Human Oral-Pharyngeal-Laryngeal Regions

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Submitted: 23 February 2015

Accepted: 19 March 2015

Published: 23 March 2015

Keywords

- Dry powder inhaler
- Static charge
- Asthma
- Aerodynamic size
- Oropharyngeal deposition

Abstract

The dry powder inhaler (DPI) is a popular, effective and convenient drug delivery device for inhalation therapy to treat asthma. However, a large quantity (approximately 54%) of inhaled aerosols deposit in the oropharyngeal region. Deposition in this region is undesirable because it provides minimum therapeutic benefits and has adverse localized or systemic side effects. This study reports a method of examining electrostatic charge effects on deposition of three DPI aerosols (Spiriva™ Handihaler, Advair Diskus™, and Pulmicort™ Turbohaler) in a cadaver-based cast of the human oral-pharyngeal-laryngeal (OPL) regions. Experimental aerosols were generated from the three commercially available DPIs by means of inhalation as boluses, and then characterized with an electronic single particle aerodynamic relaxation time analyzer with or without passing through the OPL regions. The results showed that aerosol particles were not only of different sizes but also carried different positive, negative and zero electrostatic charges. The deposition fraction of total particles (charged and uncharged) in the OPL regions for the Spiriva, Advair and Pulmicort were 22%, 61% and 7%, respectively, whereas the deposition fraction of charged particles in the Spiriva, Advair and Pulmicort generated aerosols were 62%, 67% and 28%, respectively. The inherent net charge to mass ratio were Spiriva 0.76 ± 0.11 μC/g (negative), Advair Diskus 0.49 ± 0.3 μC/g (negative), and Pulmicort 0.46 ± 0.02 (μC/g (negative), respectively. The study results also revealed that inherent charges of smaller (aerodynamic diameter, d_a < 2.0 ∝m) particles influenced their agglomeration, and therefore, increased their deposition due to inertial impaction and electrostatic space charge forces. In addition, the deposition fraction of these charged particles rapidly increased for Spiriva and Advair but marginally increased for Pulmicort with increasing particle sizes. Electromechanical properties (both aerodynamic size and electrostatic charge) play significant roles in the deposition of dry powder inhaler aerosols in the human oral-pharyngeal-laryngeal regions.

ABBREVIATIONS

DPI: Dry Powder Inhaler; OPL: Oral-Pharyngeal-Laryngeal; ET: Extra Thoracic; COPD: Chronic Obstructive Pulmonary Disease; ELPI: Electrical Low Pressure Impactor; ESPARTA: Electronic Single Particle Aerodynamic Relaxation Time Analyzer; USP: United States Pharmacopoeia; ETS: Electro-Tech Systems; CMAD: Count Median Aerodynamic Diameter; MMAD: Mass Median Aerodynamic Diameter; GSD: Geometric Standard Deviation; SD: Standard Deviation; DE OPL: Deposition Efficiency In The Oral-Pharyngeal-Laryngeal Region

INTRODUCTION

The oral-pharyngeal-laryngeal (OPL) deposition is the major determinant for lung deposition of an inhaled aerosol [1]. In order to be delivered to the target receptors of the intrathoracic lung, aerosolized pharmaceutical agents must first traverse and penetrate the extra thoracic (ET) airway (i.e., passages of the mouth and throat) [2-4]. That is, to elicit optimum therapeutic responses, medicinal agents such as bronchodilators and steroids employed in the management of asthma should be selectively distributed among lung airways. To accomplish this task, it is

imperative that the particle filtering characteristics of the ET region be acknowledged when delivering aerosolized medicines to the lungs [5].

The dry powder inhaler (DPI) is a popular drug delivery device used in the treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary diseases (COPDs), because 1) it has been shown to be effective and convenient to use, 2) it does not contain propellant and can remain with required physiochemical properties in a wide change of environmental conditions. As noted, the localized deposition of drug particles at desired sites, such as inflamed tissue, and appropriate receptors has been recognized by clinical investigators as being critical for the effective administration of asthma drugs. Approximately 54% of inhaled aerosols are lost in the oropharyngeal region [6-8]. These deposited drugs are swallowed, enter the gastrointestinal tract, and cause systemic side effects [7]. Furthermore, the low thoracic delivery efficiencies of costly drugs would be an impediment to their use [2,8,9]. It is therefore appropriate to study the particles' electromechanical properties on deposition behavior in the oral-pharyngeal-laryngeal (OPL) regions.

Several studies have found that electrostatic charge forces influence particle deposition in the ET region along with more commonly recognized forces like inertial impaction, sedimentation, and diffusion [10-17]. It is an accepted practice that most DPI formulations consist of micronized drug blended with larger carrier particles. The electrostatic interaction between drug and carrier is a major determinant of DPI performance like other attributes such as particle size, flow property, formulation, drug-carrier adhesion, respiratory flow rate, and device geometry [18]. This study employed three different DPIs with different formulations, devices, doses and manufacturers. As a result, their electrostatic charge properties were different due to the combined effects of these factors, and the effect of this charge on deposition variation in the OPL was the aim of this study.

The DPI aerosol particles acquire charges via electron and ion transfer during particle-particle and particle-device component contact and separation. More importantly, respiratory airways are conductive but do not prevent particles from charging [19]. The charge distributions (both magnitude and polarity) are dependent on the work functions of the materials coming in contact with each other, the friction and surface area involved in the contact, dielectric properties of the materials, and the ambient relative humidity. The charge magnitude is affected by numerous factors, including drug propellant surfactants, metal surfaces of delivery devices, drug/carrier homogeneities, and excipient particles size distribution [19,20]. Although, it has been standard laboratory procedure to pass an aerosol through a charge neutralizer to attain a Boltzmann equilibrium (i.e., zero net charge), a DPI aerosol has only a slight possibility to become charge neutralized before inhalation [21]. Electrostatic properties of particles consist of: (a) mutual repulsion between particles due to space charge forces, subsequently influencing agglomeration and interactions with other particles; and (b) mutual attraction between particles and neutral inner surfaces of airways due to image charge forces [19,22]. Both forces are dependent on the airborne particle number density [21]. In addition, the adhesive forces among drug particles are due to the electromagnetic forces that act between electrons and protons of the individual molecules [20]. A study with 0.6 μm carnauba wax particles showed that deposition increased from 13% to 22% when the number of elementary charges on particles increased from 2.7 to 7.5 μC [23]. Balachandran [24] reported that a low particle charge (approximately 10 μC per 2 μm particle) produced enhanced pulmonary deposition, while a higher particle charge (approximately 300 μC per particle) favored deposition in the upper airways.

In the literature it has been reported that particle sizes and device geometries affect ET losses [21,25]. However, charge acquisition due to mouth-throat turbulence and its subsequent role on deposition has not been elucidated. The major reason of this lack of information has been the unavailability of a suitable measuring instrument. Drug aerosol characterization studies have used an electrical low pressure impactor (ELPI) to analyze aerosol particle charges [26, 27]. However, the ELPI has a limitation because it provides only the net charge of all particles deposited on its impactor plate rather than for each particle in real time. To resolve this issue, this work used an electronic single particle aerodynamic relaxation time analyzer (ESPARTA) to perform electric charge measurements on a single particle basis and in real time [26]. This investigation had two specific objectives: (1) to characterize and compare the aerodynamic sizes and electrostatic charges of aerosols generated by three DPIs; and (2) to study the effects of these properties on aerosol deposition in a replica cast of the human oral-pharyngeal-laryngeal airways (Figure 1). Aerosol researchers usually employ the United States Pharmacopoeia (USP) metal throat or glass throat impinger to sample particles for characterization in an Andersen Cascade Impactor. Studies have found that the metal USP throat and glass throat impinger have significant deposition differences, and the deposition in both were lower than in vivo data [9,28]. A chief motivation for using the OPL replica cast in this study was its intrinsic similarity to in vivo airway anatomy.

MATERIALS AND METHODS

The experimental system consisted of several components, which are addressed below.

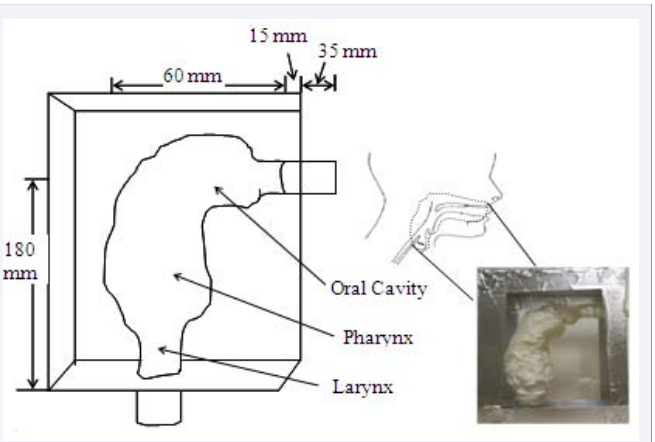

Figure 1 Cadaver-based cast of the human oral-pharyngeal-laryngeal (OPL) regions.

(i) Three delivery devices and drugs were studied. (1) DPI Spiriva™ Handihaler, drug tiotropium bromide, 18 mcg per capsule with lactose monohydrate as carrier (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA). (2) DPI Advair Diskus™ 500/50, single blister contained the drug fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder (GlaxoSmithKline, Research Triangle Park, North Carolina, USA). (3) DPI Pulmicort™ Turbo haler, each metered dose contained 200 mcg budesonide inhalation powder, but the data on excipient amount was not available. (AstraZeneca, Wilmington, Delaware, USA). Three aerosol devices were used for each type of DPIs. Even though all of the formulations contained both are active pharmaceutical ingredient and an excipient, their unequal quantities did not affect the measurement of aerodynamic diameters and electrostatic charges because the ESPARTA instrument characterized each bolus for a period of 5 minutes only (Figure 1).

(ii) The replica cast (Figure 1) was made of polyester resin. It was a life-sized model and included the continuous OPL passages of a healthy 82-year-old male subject. It was made from a post-mortem negative cast and was prepared in the Division of Pulmonary and Critical Care Medicine at the University of California, Irvine, California, USA. The replica OPL cast was placed in a controlled chamber designed to simulate the humid environment inside a human. The relative humidity was maintained above 95% with an automatic humidity controller (Model 514, ETS Electro-Tech Systems, Inc., Glenside, Pennsylvania, USA). The chamber and lab temperature were same, and it was measured 37°C by using an **Extech Heavy Duty Hot Wire Thermo-Anemometer (Extech Instruments, Waltham, Massachusetts, USA).**

(iii) The Electronic Single Particle Aerodynamic Relaxation Time Analyzer (ESPARTA) was used to measure aerodynamic sizes and electrostatic charges in real time. It was designed and developed in the Aerosol Drug Delivery Research Lab of the University of Arkansas at Little Rock, Little Rock, Arkansas, USA [26]. Its application in the area of aerosol medicine was demonstrated elsewhere [29].

*(iv)*An aerosol sampling chamber held aerosols for characterization (Figure 2). It had a volume of 28.3 liters and four ports equipped with valves (V_2, V_3, V_4, and V_5), and one pressure gage. V_2 controlled the aerosol flow from the OPL replica cast to the chamber, V_3 connected the chamber to a vacuum pump, V_4 opened the chamber to ambient air, and V_5 controlled aerosol flow from the chamber to the ESPARTA. V_1 controlled aerosol inhalation through the cast. The Aneroid pressure gauge monitored the chamber's vacuum pressure. The chambers inside walls were lined with a grounded wire mesh. Figure 2 depicts the experimental system. To characterize the DPI aerosols, Cheng proposed that bolus inhalations be employed to promote realism [30]. We adopted this methodology. Experiments started with the evacuation of the aerosol sampling chamber to 35.6 cm of mercury (0.5b) to simulate the inhalation of an aerosol bolus once the inlet valves V_1 and V_2 were opened. The inhaled volume was 4 liters over 8 seconds at a flow rate of 30 L/min. The flow rate was measured using an **Extech Heavy Duty Hot Wire Thermo-Anemometer (Extech Instruments, Waltham, Massachusetts, USA).** To characterize drug aerosols with or without passing through the OPL replica cast, the DPI devices were actuated for two experimental scenarios.

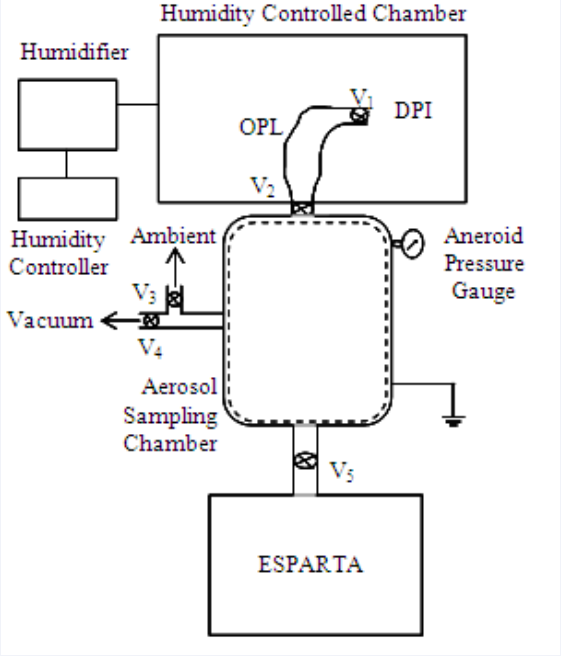

Figure 2 Schematic of the experimental arrangement designed to measure aerodynamic diameters and electrostatic charges of DPI drug aerosol particles before and after passing through the oral-pharyngeal-laryngeal (OPL) replica cast in real time. **Abbrevations:** ESPARTA: Electronic Single Particle Relaxation Time Analyzer.

Scenario 1: At the inlet of the cast the instant before opening V_1, while V_2 was open and V_3, V_4, and V_5 were closed (i.e., inhaling through the cast)

Scenario 2: At the inlet of the sampling chamber the instant before V_2 was open while V_3, V_4, and V_5 were closed (i.e., by-passing the cast)

Prior to each run in the series of experiments, the aerosol sampling chamber was vacuum cleaner and the cast was washed with distilled water. To ensure that the inner walls of the sampling chamber had the same effects on particle motion, the DPI devices were actuated at the same inlet of the aerosol sampling chamber. This supported an assumption of equal particle losses in the scenarios described above. Once the sampling chamber was filled, V_1 was shut to implement Scenario 1, or V_2 was shut to implement Scenario 2, and V_4 was opened for sampling by the ESPARTA instrument for a period of 5 minutes for both scenarios 1 and 2. It was unlikely; therefore, that a variation of drug quantity in each dose from an individual inhaler affected the measurements and comparisons of charged particles in each bolus. The procedure was repeated for 5 consecutive runs. The sizes and charge distributions were measured in each case. Raw data was acquired through Lab View (National Instruments, Austin, Texas, USA) and mined by Aerosol Particle Data Analyzer software (developed at the Aerosol Drug Delivery Research Lab of the University of Arkansas at Little Rock, Little Rock, Arkansas, USA).

RESULTS AND DISCUSSION

In order to be able to compare the electromechanical properties' effects on the deposition fraction of the generated aerosols from three DPIs, the particle aerodynamic size and charge distributions are plotted in (Figures 3-5). Figure 3 shows the comparison of the particle aerodynamic size distributions of three DPIs. The 5-minute counts without passing through the OPL cast were, Spiriva: 5923 ± 77, Advair: 5889 ± 20, and Pulmicort: 5110 ± 25 (mean ± SD). Aerosols from the Spiriva and Advair were widely distributed. The Pulmicort had a narrower distribution than the other two. Figure 4 shows the comparisons of the count median aerodynamic diameter (CMAD), and the mass median aerodynamic diameter (MMAD) of three DPIs. The CMAD and MMAD of Spiriva were 3.61 ± 0.07 µm, and 4.99 ± 0.03 µm, respectively; Advair were 3.61 ± 0.19 µm, and 5.29 ± 0.15 µm, respectively; and Pulmicort were 2.86 ± 0.02 µm, and 3.65 ± 0.1 µm, respectively. Compared to the other two, Pulmicort showed the best reproducibility result (geometric standard deviation, GSD< 0.02). Figure 5 shows the electrostatic charge distributions of three DPI aerosols. As can be seen, the Pulmicort had less number of charged particles than the other two though the share of negatively charged particles was higher for each DPI. The inherent net charge to mass ratio was also negative for all of them, e.g., Spiriva: -0.76 ± 0.11 µC/g, Advair: -0.49 ± 0.3 µC/g, and Pulmicort: -0.01 ± 0.02 µC/g. All three DPI aerosols contained both positively and negatively charged particles. Spiriva and Advair aerosol particles carried a large number of elementary charges. As a result, deposition efficiency were greatly affected (Figure 6) by their charge distributions. The deposition fraction will be defined as the ratio of the number of particles removed from the aerosol (i.e., deposited) while traveling through the replica OPL cast to the number of particles originally entering it. Table 1 shows the normalized data from 5 runs of charged particle counts and both charged and uncharged particle deposition efficiencies for each DPI. It also summarizes the count median aerodynamic diameter (CMAD), mass median aerodynamic diameter (MMAD), and electrostatic net charge to mass ratio (specific charge) for all DPI aerosols before passing through the OPL replica cast.

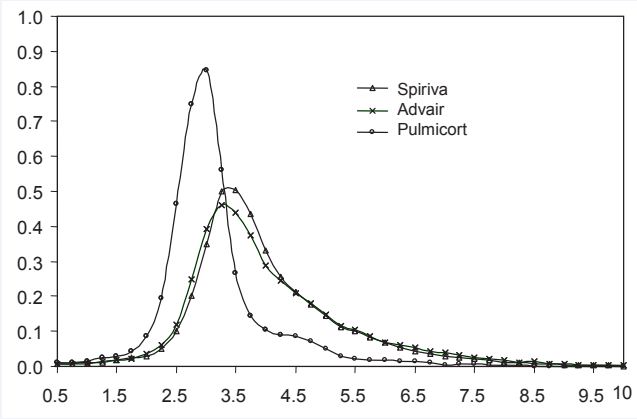

Figure 3 Particle aerodynamic size distributions for three different DPI generated drug aerosols.

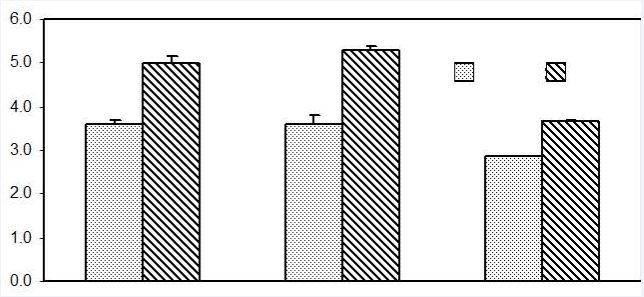

Figure 4 Particle size analysis of three different DPI generated drug aerosols (each bar represents mean ± SD).
Abbrevations: CMAD: count median aerodynamic diameter; MMAD: mass median aerodynamic diameter

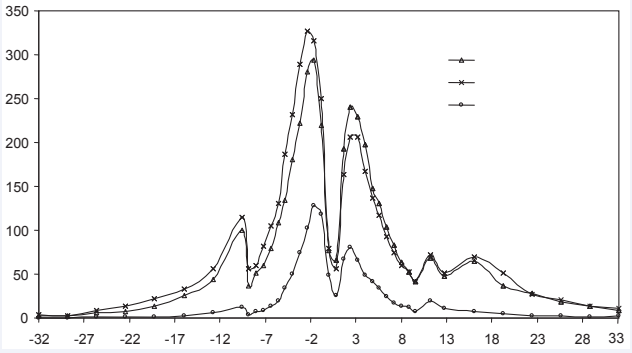

Figure 5 Particle electrostatic charge distributions of three different DPI generated drug aerosols.

As can be seen, oral-pharyngeal-laryngeal deposition of all (charged and uncharged combined) particles of three DPIs were, Spiriva: 22%, Advair: 61%, and Pulmicort: 7%. Comparing the deposition patterns of charged and uncharged particles, it was observed that the uncharged particles deposited much less efficiently than the charged particles. Uncharged particle depositions were, Spiriva: 34%, Advair: 51%, and Pulmicort: 8%, whereas, the charged particles depositions were, Spiriva: 68%, Advair: 67%, and Pulmicort: 28%. Some significant differences in the deposition efficiencies between different polarity particles were also observed. More negatively charged

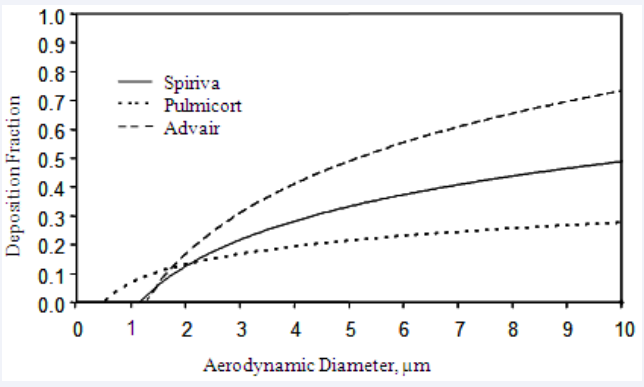

Figure 6 Comparison of the oral-pharyngeal-laryngeal deposition fractions of the three dry powder inhaler aerosols.

Table 1: Summary of the laboratory data.

Drug Delivery Device	[1]DE OPL [5]All particles Uncharged Charged	% of Charged + counts - counts	[2]Net q/m + ve q/m - ve q/m (µC/g)	[3]CMAD (µm) [5]All particles St. Dev.	[4]MMAD (µm) [5]All particles St. Dev.
Spiriva™	22% 34% 68%	62 % 1,783 1,899	- 0.76 + 5.30 - 6.61	3.61 0.07	4.99 0.03
Advair™	61% 51% 67%	67 % 1,626 2,313	- 0.49 + 4.77 - 6.30	3.61 0.19	5.29 0.15
Pulmicort™	7% 8% 28%	28 % 475 618	- 0.46 + 5.47 - 6.63	2.86 0.02	3.65 0.10

Abbreviations:
[1]DE OPL = Deposition efficiency in the Oral-Pharyngeal-Laryngeal Regions
[2]Net q/m = Net charge/mass ratio
[3]CMAD = count median aerodynamic diameter
[4]MMAD = mass median aerodynamic diameter
[5]All particles = both uncharged and charged particles

particles were deposited than were their positive counterparts. For example, deposition of positive and negative particles of Spiriva were 45% and 87%, respectively; Advair were 57% and 74%, respectively; and Pulmicort were 0.2% and 54%, respectively. Figure 6 represents the OPL cast deposition fraction as a function of particle aerodynamic size, which shows how the charged properties affected the deposition patterns. Although the deposition fractions were increased linearly with increasing particle size for all DPIs, the rate of increase was highest for the one which contained the largest percentage of charged particles. The generation of aerosols from a DPI depends upon 1) the integration of inhaler design, 2) the drug and carrier powder mixture formation, and 3) patient's inspiratory effort. In this study variable 1 and variable 2 are differed among the tested DPIs. Therefore the difference in deposition observed in the present study could be due to differences in design of inhaler devices, flow properties, excipients, or active ingredients in addition to electrostatic charge and particle size.

The study results of this work showed the Spiriva had the highest number of charged (67%) particles, of which 41% were positive and 59% were negative. The Adavair had the second highest number of charged (62%) particles, of which 48% were positive and 52% were negative. Hence, there were two electrostatic force situations. First of all, the uni-polar charged particles induced greater space charge forces and mutual repulsions. As a result, particles came closer to cast walls and were captured. Secondly, bi-polar charged particles agglomerated due to Coulombic attraction forces, which allowed smaller particles to become larger and deposit more efficiently within the cast due to inertial impaction. The agglomeration due to electromagnetic forces is consistent with Finlay's theory [20], and the increased impaction (due to formations of larger sizes) is consistent with the findings of Yu and Diu [31]. In contrast, the Pulmicort had a relatively small amount (28%) of charged particles, of which 43% were positive and 57% were negative. As a result, very little agglomeration took place, and the aerosol losses on cast walls were comparatively low (7%). During the inhalation of an aerosol bolus, a complicated inlet velocity profile and flow conditions in the OPL replica cast may have affected the abilities of particles to gain electrostatic charges through tribo-electric charging processes [16,32]. Electrostatic charge forces had major influences on the deposition properties of all DPI aerosols. These influences were an indication of enhanced charged particle deposition in the cast. Therefore, it can be summarized that overall deposition efficiencies of charged particles were higher than uncharged particles. This observation agrees with Yu's [22] mathematical model and the experimental studies done by Hashish et al. [13] and Cohen et al. [14]. One study reported that surface modification of carrier/excipient particle can be reduced by using force control agents such as Plurionic F-68, Cremophor RH40, soya lecithin, glyceryl monostearate, and magnesium stearate [33]. Such attempts may reduce the gaining of high charges of the aerosolized particles.

In this study, it is logical to recognize certain limitations. It purposely avoided particles smaller than 0.5 µm because the ESPARTA was not able to detect sizes below this limit; the OPL replica cast was made of polyester resin; and it also assumed a uniform state of temperature and humidity within the replica cast; and no growth or evaporation of particles in transit. Within this framework, this study did identify and quantitate the inter-related effects of electrostatic charges and particle sizes on the deposition of various DPI aerosols. It is believed that the study findings have practical values and clinical implications and suggest that the developers of aerosol drug delivery devices consider electrostatic charge effects while designing future improved products.

CONCLUSION

In conclusion, this study demonstrates the electromechanical properties (both aerodynamic size and electrostatic charge) significant roles in the deposition of aerosols in the human oral-pharyngeal-laryngeal regions. The DPI aerosol deposition in the OPL region (often refers as extra thoracic region) is much less for the drug delivery device that generates fewer charged aerosols than for the others, a fact which clinicians may choose to consider in inhalation therapy protocols.

ACKNOWLEDGEMENT

The author would like to thank Emeritus Professor Malay K. Mazumder of the University of Arkansas at Little Rock, Arkansas, USA for enabling to use the ESPARTA instrument for conducting this study.

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Cite this article

Ali M (2015) Effects of Three Dry Powder Inhalers on Deposition of Aerosolized Medicine in the Human Oral-Pharyngeal-Laryngeal Regions. J Drug Des Res 2(1): 1009.