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Experimental and numerical study of nasal spray characteristics and its application in a realistic human nasal cavity

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Abstract

The nasal spray characteristics and its drug delivery efficiency in a realistic human nasal cavity was studied in this paper. Commercial pharmaceutical nasal spray devices were utilized for spray formation under physiologically reasonable actuation force. External spray plume characteristics such as the spray cone angle and break-up length were captured via particle/droplet image analysis (PDIA) approach. Numerical spray simulations were conducted by utilizing those experimental data as boundary conditions, where the nasal spray device was inserted into a realistic adult nasal passage. $k-\omega$ SST model was used to predict the transitional turbulence flow. The spray direction was aligned with the centerline of the nasal valve to avoid unnecessary early droplets deposition in the vestibule. Particle delivery efficiencies of selected micro-particle size (5 µm, 10 µm, 15 µm, and 50 µm) were assessed. The results demonstrated that the narrowed vestibule channel structure significantly constrained the development of the spray plume, and considerable amount of particles were blocked due to the limited droplets travelling space. For large sized micro-particles (name the size value), inertia dominates their fly paths, and particles were deposited shortly after releasing, while for the small sized particles (name the size value), they can follow the airflow streamlines and travel further downstream due to the reduced inertia effects; however, more particles would pass through the nasal turbinate and may deposit into the lungs, which is harmful as well. This study demonstrated a combined experimental and numerical approach for the better acknowledgment of nasal spray iterations with realistic human nasal cavity. The proposed combined approach can improve the design of future nasal drug delivery devices, and benefit more patients with elevated drug delivery performance.

Themes: Computational fluid dynamics; biomedical fluids

Introduction

A spray is [14] "a dispersion of droplets with sufficient momentum to penetrate the surrounding medium". In another expression, in term of the mechanical field it is a continuous motion to transfer bulk liquid into droplets under force/pressure through a reduced area like an orifice apart from the natural sprays which includes sea fog, rain, waterfall mist, and etc. The main reason why spray is utilized in various industries is the increment of the surface area like the oil aerosol inside combustion engines, however, this is at approximately 100 bar [2], and meanwhile the relevant study of low pressure applications lags behind, the near past studies disclosed the relationship between droplet size/spray angle and nasal penetration depth where the larger droplet size and wider cone angle could not reach the targeted nasal cavity [4]. Moreover there remains a great difficulty to experimentally measure the spray flow in the near-nozzle region to understand the mechanism of the atomization process. Apart from this there are several experimental studies regarding to the nasal cavity deposition both in vivo [9, 10] and in vitro [8, 12, 16] method. Based on these studies the deposition efficiency associates with the characteristics of spray flow, i.e. liquid density, flow rate, particle size, and etc. Unfortunately the experimental set-up utilize an extended pipe to introduce the suspended particles into nasal cavity, this could not mimic the real inhalation with sprayed particles. With the increase in computing power embedded with advances numerical algorithms an alternative approach to match in vivo experimental data is to use computational techniques such as computational fluid dynamics (CFD). Via the ability to calculate extreme physical conditions such as the air velocity profile [13], particle trajectories and localised deposition sites [15], CFD techniques was already used in these past studies that concentrated in the inhalation of suspended particles in the air [7]. Therefore, CFD could be used in even advanced application to investigate the external characteristics of nasal spray and the real physical deposition pattern/efficiency numerically. Fortunately the qualitative experimental study aimed to provide result such as droplet size, velocity, 1st break-up length that could be utilised to form the key elements in boundary condition in CFD simulation. In this way this study would unveil the real particle deposition mechanism in real physical condition numerically with a mimicked illustration in vivo experiment, thus to help the pharmaceutical industry to optimise the delivery method, and then to benefit patients.

Methodology

Experimental Set-up

The objective of this experiment is to capture the outline of the spray cone during the fully developed stage and within the region between nozzle and 1st break-up length, thus in order to achieve this purpose High Speed Camera (HSC) and spotlight were utilised. As illustrated in Figure 1 (a) the experiment set-up could be divided into two parts which are recording section and actuator section. For the recording part, HSC and spotlight are positioned in a line but opposite direction, an auto trigger zone was set right above the nozzle to detect the slight movement of spray

beam via the built in software of HSC. For the Pneumatic actuator part, the actuator was held in the base which could be pushed up and down by Programmable Logical Controller (PLC). Thus under this protocol two common commercial brands of nasal sprays were selected to conduct the experiment, in order to gain better accuracy 16 tests were conducted for each brand. Ahead of filming procedure a pre-experiment was done and the purpose is to imitate the real human physical actuation. In order to match the real physical actuation, firstly a set of real human physical test result should be obtained to be used as a datum, based on this Data Acquisition System and strain gage were introduced to record the strain change of nasal spray bottle while actuating, thus a strain gage was glued vertically on the upper bottle exterior surface wall. The whole procedure was divided into 2 steps which were illustrated in Figure 1 (b). The first one is with hand to get the average human actuation parameters, and the second one kicked in with actuator controlled by PLC (3 variations, i.e. controlled input pressure valve, inlet speed controller, and outlet speed controller) and solenoid control valve [1] to mimic the result gained in previous step.

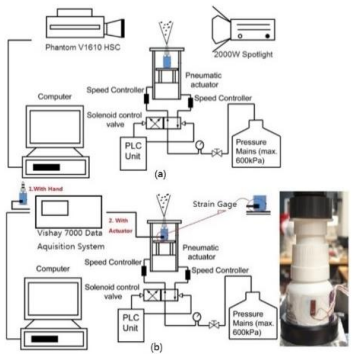

Figure 1**.** (a) Schematic of Experimental Setup for filming spray outlines, (b) Schematic of Experimental Set-up for matching study and a snapshot of glued strain gage

Numerical Set-up

Real nasal cavity geometry was gained via CT scan images of a human (48 year old healthy Asian male) for both left and right nasal passages and nasopharyngeal [11]. Then this model was truncated at the anterior trachea to concentrate on the upper respiratory tract where the nasal spray medication targeted and passed, and the reconstructed airway from CT scan could be seen in the Figure 2 below. This model was an upgrade and correction from previous study model [5, 6] to present the flow conditions in the near nostril inlet region in a more detailed and real scenario, and the improvement included the external nares, facial features, inserted nasal spray bottle (one nostril closed), and the ambient air environment next to face. The whole computational model was meshed by using ANSYS® USA with unstructured tetrahedral elements, and Prism layers were applied in near wall regions to provide accurate wall behaviour on droplet. The independent mesh elements for human were 4 million with the detailed multi-layer near wall meshing. As shown in Figure 3 it is found that the vestibule passage width continuously narrows down from the nostril to the nasal valve while the length elongates, furthermore the nasal valve is the main restriction for the spray plume propagation due to its narrowed anatomical structure. To optimize the spray nozzle - nasal valve alignment, a spray nozzle adjustment plane was proposed. The spray nozzle was aimed at the centre line of the nasal valve, and its aiming direction is adjustable within the nozzle angle adjustment plane. Angle α and β indicates the upwards and downwards angle adjustment allowance respectively.

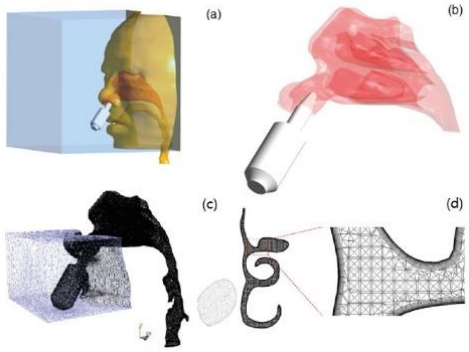

Figure 2**.** (a) Modified model with an adult male face, ambient air, (b) Nasal cavity with a spray bottle inserted into nose, (c) Meshing for 4 million cells, (d) The near wall multilayer meshing

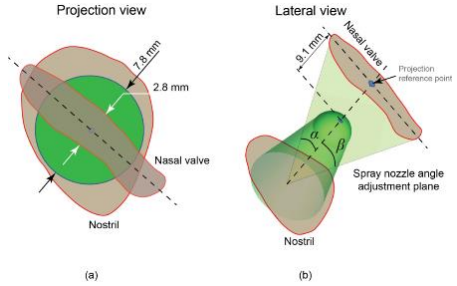

Figure 3**.** The alignment of the spray nozzle and the nasal valve with adjustment angle

Result and Discussion

Spray characteristics

The average real human physical profile is with a 450 micro-strain drop and approximately 800 ms duration, then this was set as the datum to let the machine actuation result match on, as a result 3.25 bar with 8.5 turns on inlet speed controller and 11 turns on outlet speed controller was the best mimic as seen in Figure 4. As shown in Figure 5: the basic spray cone shape of Brand-D is with a nozzle orifice radius of 0.35 mm, first break-up length of 2.5 mm, and first break-up radius of 2.5 mm, hence the spray cone angle is 80°; the basic spray cone shape of Brand-P is with a nozzle orifice radius of 0.2 mm, first break-up length of 3.3 mm, and first break-up radius of 2.1 mm, hence the spray cone angle is 60°; all these parameters were used as the input in CFD simulation.

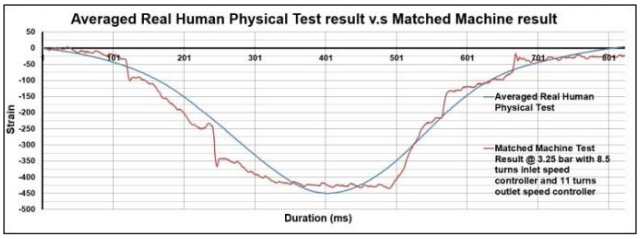

Figure 4**.** Averaged real human physical test result vs. matched machine result

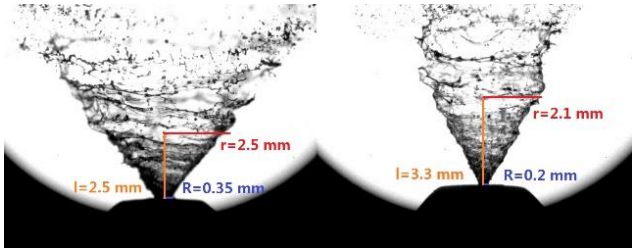

Figure 5. Break-up length, break-up radius, and nozzle orifice radius for two brands

Particle deposition efficiency

Figure 6 and Figure 7 demonstrate the difference between laminar (nostrils both open) and turbulent flow (right nostril closed). There are several difference between two methods. The first one is the air flow in right passage, the conventional method shares a similar air flow pattern with the left passage, but in the current method only the opened nostril fulfilled with air flow field whereas the closed right nasal cavity has a bit recirculation flow from the vortices in pharynx and larynx region due to the high speed turbulent air flow. The second one is the velocity variation, the air flow velocity (up to 6 m/s) in conventional method is much lower than the current method especially in the targeted middle section region (up to 12 m/s). The third noticeable difference is that there are more air flow circulation in olfactory region in current method than the conventional one. The fourth one is the airflow pattern difference in pharynx and larynx region, the current method has a large amount of vortices but the laminar flow dominates the conventional one.

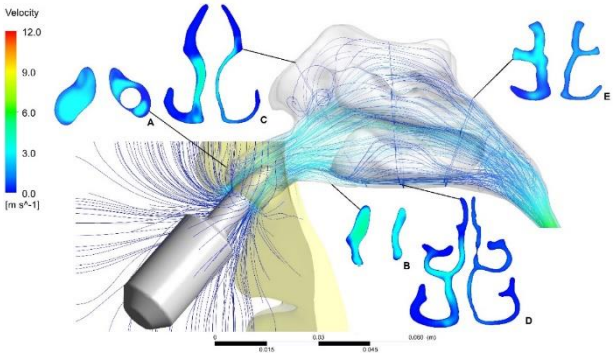

Figure 6**.** Nasal cavity streamlines in the drug administering in both cavities with five cross sectional velocity profiles

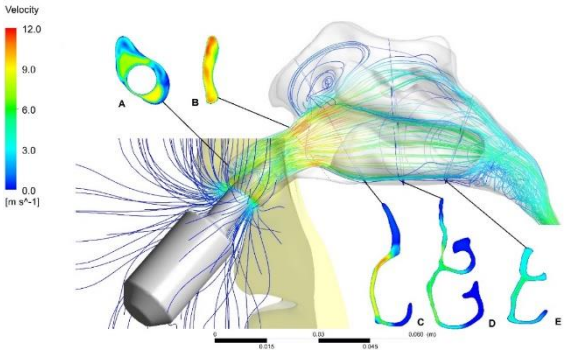

Figure 7. Nasal cavity streamlines in the drug administering in single cavity with five cross sectional velocity profile

Figure 8 illustrates the comparison of different injection orientations between laminar and turbulent flow for Brand-D and Brand-P of different released particle sizes in lateral region. Two conclusions could be drawn from this cross comparison, the first one is for the same spray cone angle the particle deposition fraction in lateral region for turbulent case is higher than the one of laminar flow no matter of particle size, and the second one is for both laminar and turbulent flow the particle deposition in lateral region the narrower spray angle would result in a better deposition fraction than a wider spray angle spray cone, i.e. in term of drug delivery performance Brand-P is much better which means less drug would be wasted after atomization. Figure 9 demonstrates the comparison of different released particle sizes between laminar and turbulent flow for Brand-D and Brand-P in different injection directions in lateral region. The maximum deposition fraction is 44% of all case studies which all happen in OC direction for 10 µm, and 15 µm. Thus the most important finding is OC injection trajectory appears to be the best drug delivery path inside nasal cavity.

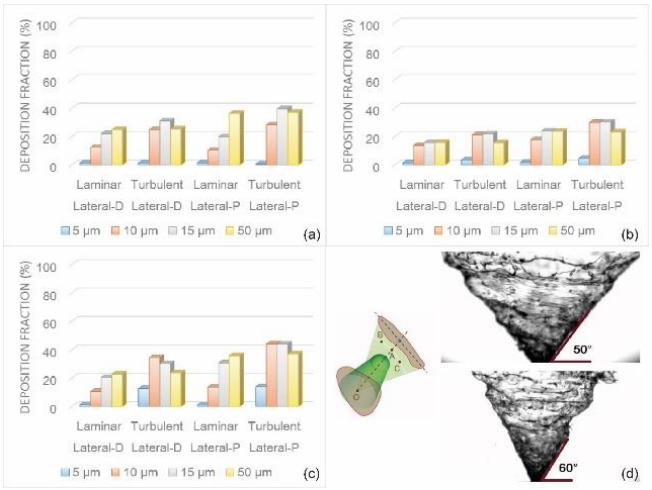

Figure 8. Turbulent Deposition fraction in Vestibule and Lateral region for Brand-D and Brand-P of 5 µm, 10 µm, 15 µm, and 50 µm in injection trajectory of (a) OA, (b) OB, (c) OC, and (d) Spray cone angle indication for Brand-D and Brand-P

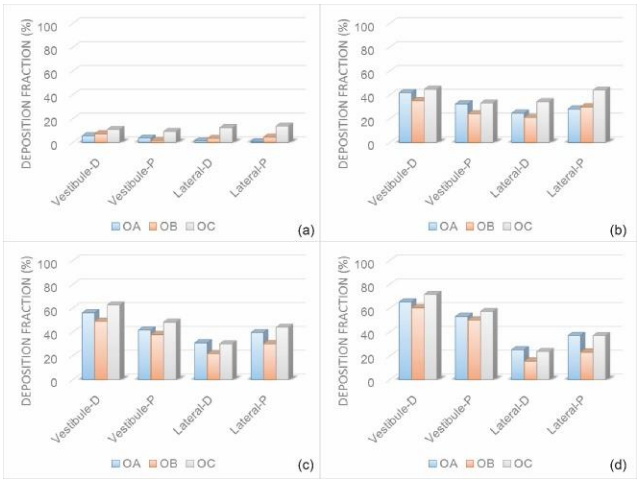

Figure 9. Turbulent Deposition fraction in Vestibule and Lateral region for Brand-D and Brand-P in OA, OB, and OC injection trajectory of (a) 5 µm, (b) 10 µm, (c) 15 µm, and (d) 50 µm

Conclusion

In experimental study the real human actuation profile was obtained and mimicked by in-house experimental equipment; then by utilizing the high speed filming technique the detailed nasal spray atomization procedure was captured; and later Sobel function via MATLAB® and visual inspection was used in the post analysis to acquire the basic spray cone parameters of Brand-D and Brand-P, i.e. spray cone angle, first break-up length, and the spray cone diameter; at last all these parameters were used as the input in CFD simulation. In numerical investigation the real human nasal cavity model with ambient air and real inserted nasal spray bottle inside nasal cavity and real atomization parameters achieved from experimental study were used as the first time in history. The $k-\omega$ SST was introduced to solve the transition / low turbulence issue, and five mono-dispersed particles (5, 10, 15, and 50 μm) under a breathing rate of 15 L/min were studied to analyse the drug delivery efficiency in the targeted area, i.e. turbinate, meatus, and olfactory region. After considering all influence factors which are spray angle, injection trajectory, particle size, and flow field type, it seems that the optimal combined spray setting regarding to particle deposition fraction and drug delivery efficiency is as followed: narrower spray angle ($<60^\circ$), 5 μm to 15 μm sized particle, and turbulent flow field (one nostril closed) are preferred. This is mainly attributed to the preferred particle relaxation time, preventing the medication agents in this size from direct impaction at the vicinity of nasal vestibule region and maximizing the deposition in the main passage. The previous study has investigated the spray size distribution under different actuation pressures, and the results showed that higher actuation pressure produces smaller droplets in the atomization. Despite different actuation pressure varies from 2.05 bar to 2.65 bar [4] were applied, the volume fraction of particles smaller than 50 μm was less than 5% compared with the volume fractions of other particle sizes within the whole recorded particle size spectrum ranges from 0 to 400 μm, thus the percentage of ideal particle size from 5 μm to 15 μm is even smaller[3]. Therefore, although particle deposition fractions of selective particle sizes were reported in the presented study, additional interpretation efforts are needed in the overall performance assessment of nasal spray devices.

Acknowledgement

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