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# Aerodynamically driven translocation of non-Newtonian fluids: the relevance for intranasal drug delivery

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Intranasal drug delivery depends on the effective and possibly homogenous application of medical solution on the whole surface of nasal cavity (NC). As known from previous studies, droplets of sprayed medicine administered from an atomizer can penetrate only to the very anterior parts of the NC. This study demonstrates the possibility of translocation of liquid droplets due to interactions with air flowing through a shallow channel used as a model of nasal airspaces. The liquids used in the study are non-Newtonian to simulate the properties of real pharmaceutical formulation used in modern nasal drugs. The experimental data confirmed that aerodynamic shear forces induced by the airflow facilitate translocation of droplets of non-Newtonian fluids along the horizontal channel and this displacement is characterized by dynamic motion of droplets, in contrast to a steady spreading observed in the case of a viscous Newtonian fluid. The displacement pattern depends on the rheological characteristics of liquid, airflow rate, and also on the wettability of the wall. The results obtained in this study indirectly confirm that the inhalation airflows in the nasal channels should allow to spread the deposited liquid drugs to the distal parts of NC, providing the mechanism of more homogeneous drug distribution on the nasal surface.

## 1. Introduction

The nasal route of drug delivery is very important in treating allergy and inflammation of upper airways, and spraying is the most convenient way of drug administration to the nose (Fokkens et al., 2013; Meteran and Backer, 2016). However, it has been recognized that spraying leads to uneven distribution of deposited drugs in the nasal cavity (Jang and Kim, 2016), mainly due to the complex nasal geometry (narrow airspaces) and spray properties that are incompatible with this geometry (spraying angle, droplet velocity - Sosnowski and Rapiejko, 2017). It has been hypothesized and partly confirmed that the liquid in the form of a layer or single droplets sitting on the inner surface of the nasal cavity (or the nasal septum) might be transported to deeper regions due to aerodynamic interactions induced by air drawn during inhalation or sniffing (Sosnowski et al., 2020), as schematically shown in Figure 1. This process may serve as an explanation of drug efficiency in the whole nasal cavity despite very localized initial deposition of the sprayed droplets.

The aim of this work is to demonstrate how such aerodynamic interactions may displace liquid droplets through a channel that roughly represents the geometric features of the nasal airways. We focused on non-Newtonian fluids since they are currently used in new formulations of nasal sprays for minimization of the gravitational drainage of deposited drugs (Koźmiński and Kupczyk, 2015). The results were compared to a Newtonian fluid.

## 2. Materials and methods

Colloidal aqueous suspension composed of carboxymethylcellulose sodium salt (CMC - Merck) and crystalline microcellulose (MIC - Avicel PH-101, Merck) were used as model non-Newtonian fluids, while glycerol aqueous solution (70% v/v) was used as a reference Newtonian fluid (viscosity: 0.03 Pa s). The non-Newtonian liquids were prepared as follows: the powders of CMC and MIC were mixed at a 15:85 ratio (w/w). Then this dry mixture was mixed with water and homogenized to obtain the total concentrations: 7.5%, 10%, and 12.5% (w/v). CMC was completely dissolved while MIC formed microsuspension in this solution. The rheological characteristics of these non-Newtonian fluids were measured with Anton Paar MCR 102 oscillation rheometer in a plate-plate measuring system (25 °C).

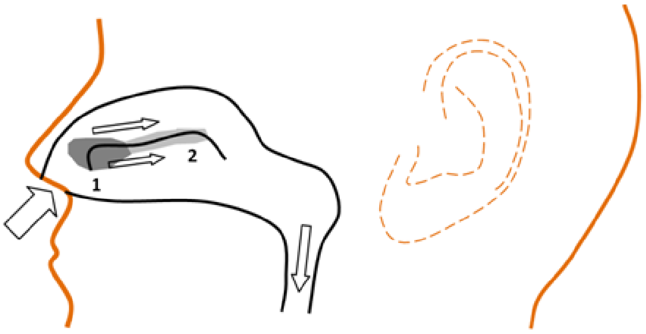

*Figure 1: The concept of the displacement of the liquid drug initially deposited in the constrained anterior location (1) to more distal regions (2) of the nasal cavity due to aerodynamic forces.*

The experiments were done in a rectangular glass channel (10 ×1 mm, length: 80 mm). The upper glass cover was equipped in a circular opening for the connection of the airflow, Figure 2. The surface of the channel was hydrophilic (i.e. wetted by the liquids) however, some experiments were done when the surface was hydrophobic due to covering by a thin layer of oily grease. The filtered air was supplied from the central compressor through the pressure gauge (1.5 bar) with the flow controlled via the needle valve and measured with the digital flowmeter (TSI Inc. USA, model 3063). The liquid samples were pipetted to the bottom of the channel below the opening in the cover, and the displacement pattern of the sample was video-recorded (SJ 4000 Cam, PRC) at full HD and 30 fps. The recordings were analyzed with several freeware applications under Windows 10. The raw frame from a captured video is shown in Figure 3. Non-Newtonian liquids were milky-white and were filmed on black background. Glycerol solution was coloured with a few crystals of methylene blue and filmed on white background. Two cases were analysed:

a) single droplet deposited on the bottom of the channel,
b) single droplet forming a bridge between the upper and lower surface.

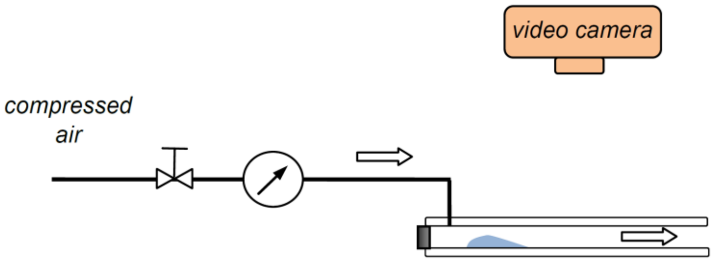

*Figure 2: Experimental set-up for liquid displacement in a shallow channel.*

## 3. Results and discussion

### 3.1 Rheometry of non-Newtonian liquids

The rheological characteristics of both CMC+MIC suspensions are shown in Figure 4. It can be seen that the liquids are shear-thinning (Figure 4a), however, they also demonstrate visco-elastic effects (Figure 4b) with increasing elastic properties at higher frequencies of shear. After fitting the Ostwald-de Waele model to describe purely viscous properties of the liquids, the consistency index *k* was found to be equal to 0.259 and

2.035, and flow behaviour index $n$ - to be equal to 0.87 and 0.74 for 7.5% and 12.5% CMC+MIC aqueous suspension, respectively (fitting coefficient: $R^2 = 0.999$ and 0.997, respectively).

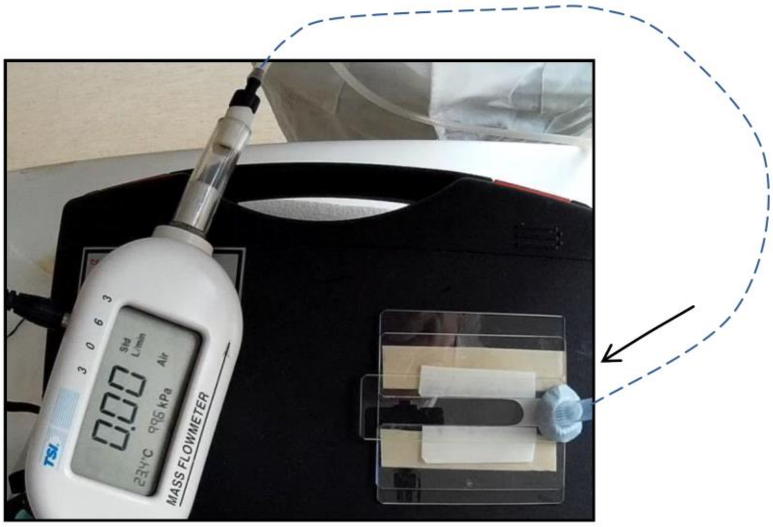

*Figure 3: The basic video frame captured during the measurement. The dashed line shows schematically the hose for air delivery to the channel.*

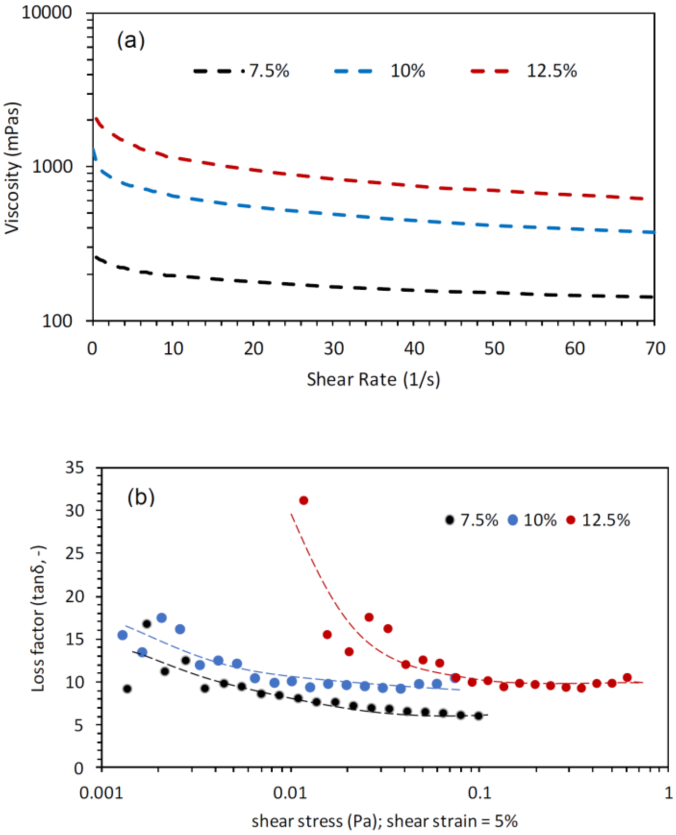

*Figure 4: (a) the apparent viscosity and (b) the loss factor measured during frequency sweep of tested non-Newtonian liquids (concentrations of CMC+MIC aqueous suspension shown in the figures).*

### 3.2 Droplet displacement in the shallow channel

Translocation patterns of non-Newtonian fluid droplets along the channel due to the aerodynamic forces are shown in Figure 5 (CMC+MIC 7.5%: slow and fast airflows) and 6 (CMC+MIC 12.5%, slow airflow). Each picture shows the evolution of droplet position and shape during flow (from left to right, i.e. starting from the picture with letter A). Note that all pictures are rotated: the channel was horizontal as seen in Figure 2, so the gravity had no influence on the liquid motion.

The influence of non-Newtonian properties on droplet displacement pattern can be easily found from the comparison of Figures 5ab and 6ab with Figure 6c. The droplet of Newtonian fluid is homogenously smeared along the channel by the aerodynamic forces (Figure 6c), as shown in other studies (e.g. Fan et al, 2011). In contrast, droplets formed by non-Newtonian fluids are moving with a continuous deformation of their shape and bouncing, and this dislocation pattern depends on the value of aerodynamic stresses, rheological properties of the liquid, and surface characteristics of the bottom wall. Higher airflows induce stronger forces acting on the droplet leading to an easier flow (partly, due to shear thinning properties of the liquid), but also to droplet deformation. This deformation also changes the airflow resistance in the channel, so the distribution of stresses in the channel cross-section is time-dependent even for the constant airflow rate. This induces dynamic effects during droplet displacement (visible e.g., in Figures 5a, 5b).

It should be also noted that when droplet deformation is more dynamic, the elastic properties of the liquid come into play, and this results in the “jumping” effect during in droplet motion (see. e.g. Figure 5b, panels E-H). The spreading of the liquid is easier when the bottom surface is wetted easily by the aqueous suspension if compared to the situation when this surface is hydrophobic - Figure 6a. When the droplet is pushed on a non-wetted surface, additional (capillary) forces retard its motion and also influence the droplet shape.

There is a striking difference in the behaviour of droplets of 7.5% and 12.5% CMC+MIC suspensions under high aerodynamic stresses (airflow: 3 $dm^3/min$) – Figures 5b and 6b. For a more concentrated (12.5%), i.e. more viscous liquid, high aerodynamic stresses cause the initial displacement of the droplet along the channel via splashing (Fig. 6b, panels B-F) and after that - by liquid smearing on the bottom wall of the channel. This can be explained by strong resistance of a droplet to the deformation induced by aerodynamic forces, which eventually results in droplet detachment from the surface (for a similar effect see Basu et al, 1997). For a less viscous liquid, the droplet deforms and is pushed along the channel. In any situation, the liquid is smeared on the bottom wall, leaving a thin layer behind the moving droplet. As a consequence, the volume of the drop is gradually reduced during displacement which increases the cross-section area for the airflow along the path if droplet displacement. Therefore, the aerodynamic interactions with the droplet are also reduced along the channel.

It should be noted that, contrary to the situation where the droplet of Newtonian liquid interacts with air at low Reynolds-number flows (e.g. Dimitrakopoulos and Higdon, 2007), there has been not much research on the discussed effect for non-Newtonian fluids at intense, possible non-laminar airflows. Adapting the presented results to the behaviour of drug droplets on the nasal surface after their administration from atomizers, it is evident that displacement of the deposited drug to more distal regions of the nasal cavity is possible due to inhalation or sniffing, even for non-Newtonian and very viscous drug formulations. It may be noted that such physiological flows are inherently non-steady (Sosnowski et al., 2006), so the dynamic effects during liquid displacement will be even more evident. The hydrophilic character of the inner surface of the nose due to natural covering by the mucus layer should facilitate deeper penetration of drugs. The transport is also possible when deposited liquids fully block the narrow air channel, i.e. when they form the liquid bridge, however, this requires further studies.

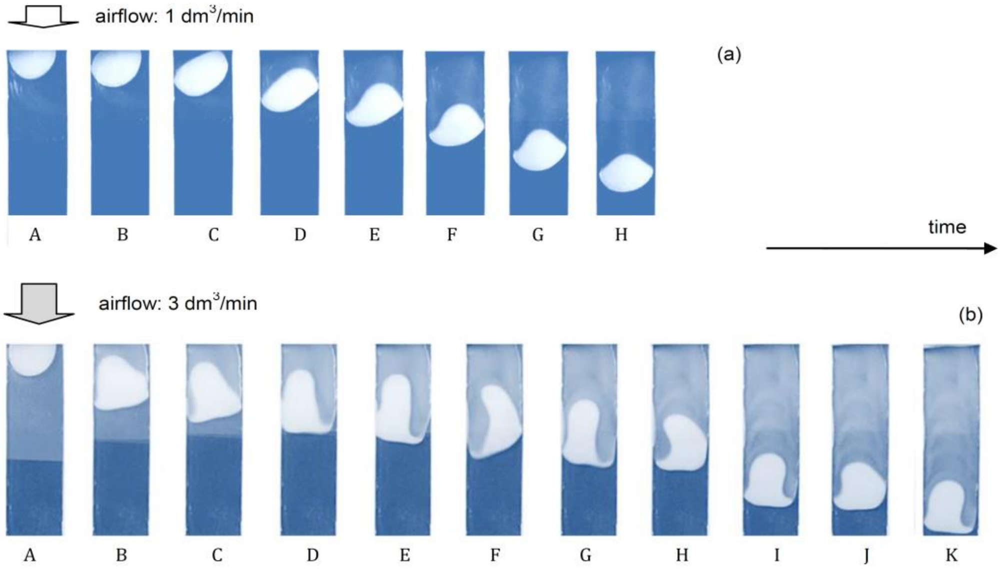

*Figure 5: Displacement of a droplet of CMC+MIC 7.5% at two airflows: (a) 1 dm$^3$/min, and (b) 3 dm$^3$/min.*

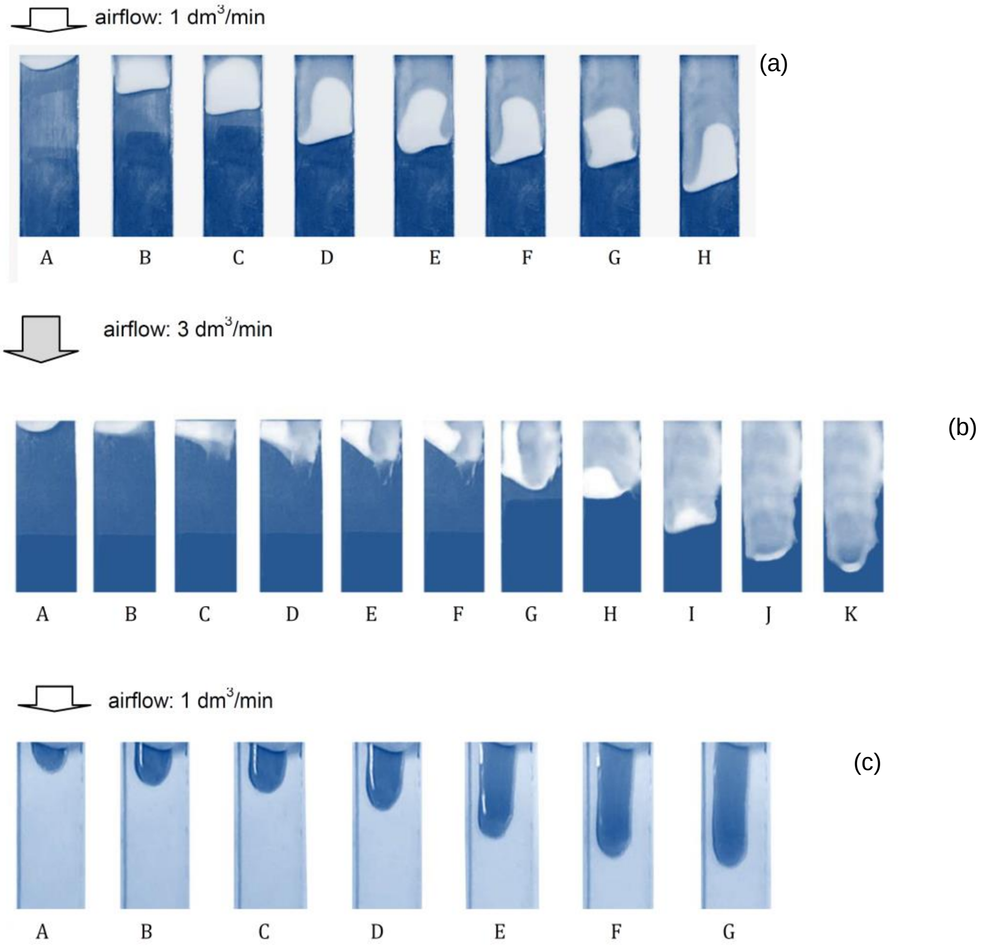

*Figure 6: Displacement of a droplet: (a) CMC+MIC 7.5% on hydrophobic surface (airflow: 1 dm$^3$/min); (b) CMC+MIC 12.5% (airflow: 3 dm$^3$/min); (c) glycerol 70% aq. (airflow: 1 dm$^3$/min).*

## 4. Conclusions

Experimental analysis in a model system showed that droplets of non-Newtonian fluids deposited on a bottom of a shallow horizontal channel are effectively pushed by the aerodynamic forces induced by the airflow. The droplets show a complex dynamic motion due to the interplay between aerodynamic shear stresses and viscous (or visco-elastic) deformations of the droplets followed by their motion along the surface. Due to droplet jumping and bouncing in the channel, the airflow pushes it in a significantly different way comparing to droplets of Newtonian fluids. It is an interesting process in the view of the possibility of dislocation (transport) of deposited liquid drugs on the surface of the nasal cavity and surely needs more investigation to evaluate the importance of this effect for the redistribution of therapeutics administered to the nose.

### Acknowledgments

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