The viscous limit for Soft Mist Inhalers; an in-silico study.

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Summary

When increasing the dose delivered by means of an SMI, the concentration of the API in the solvent is increased and thus the viscosity of the solution is increased as well. In this work the relation between the viscosity and density of the solvent and the pressure applied by the SMI is investigated. In order to generate jets with sufficient kinetic energy that create sufficiently small droplets, a lower limit for the Reynolds number of 250 is proposed. Below this limit the pressure needs to increase proportionally to the viscosity. Under the assumption that an SMI can apply a pressure of maximally 400 bar, maximal mole fractions of PEG 400 and water mixtures of 3.4 %, 4.1 % and 4.6 % for 25 °C, 30 °C and 35 °C respectively were derived to aid interpretation of these values.

Key Message

The relation of the viscosity and density of a solvent and the pressure applied by an SMI is investigated. This allows to estimate a viscosity limit and hence the maximal API, excipient or co-solvent concentration.

Introduction

Soft Mist Inhalers (SMI) offer a propellant-free method of delivering drugs to the lung. To create small droplets, energy to overcome the surface energy is required. In the case of impinging jets, this energy is delivered at the impingement point, in the form of kinetic energy of the jets. The fluid in the jets is accelerated in the nozzle by a mechanical system where a spring is used to generate pressures of typically 250 bar [1]. However, due to viscosity, energy gets lost while squeezing the fluid through the nozzle's small exit channels.

When it is intended to increase the dose, the Active Pharmaceutical Ingredient (API) concentration in a given solvent is increased, possibly along with excipients and co-solvents, and therefore the viscosity of the solution is likely to increase as well. Therefore understanding the effect of viscosity is important to understand the viscosity imposed limits on the maximal dose that can be delivered with a single shot of an SMI, while maintaining acceptable delivery performance. Besides the concentration of the API, temperature can also have a strong effect on the viscosity of aqueous solutions, *e.g.* in the range from 10 °C to 30 °C, the viscosity of water drops from 1.31 mPa·s to 0.80 mPa·s [2].

In this work we aim to understand how viscosity affects the energy available for droplet formation. The known asymptotic effects for small Reynolds numbers will be interpreted in the case of SMIs. This will allow to specify the limits applying to SMIs.

Materials and Methods

Computational Fluid Dynamics (CFD) simulations were performed by means of an in-house developed routine. The program was written in MATLAB® (Mathworks Inc) and applies the Galerkin method to solve the stationary Navier-Stokes equations [3] in the nozzle's geometry. Based on Poiseuille flow the flow perpendicular to the nozzle's plane is assumed to be 0 and the profile in this direction is assumed to be parabolic: $\boldsymbol{v}(z) = \boldsymbol{v}(0)(1 - 4z^2/Z^2)$, where $\boldsymbol{v}$ is the two-dimensional velocity vector, z is the coordinated perpendicular to the nozzle's plane and Z is the etching depth. Second derivative towards z of the velocity is given by $\partial^2\boldsymbol{v}/\partial z^2 = -8\boldsymbol{v}/Z^2$. The resulting model represents the three-dimensional model by taking into account the viscous effects of the finite depth of the nozzle, while only inquiring the computational cost of a two-dimensional model:

$$-\mu\nabla^2\boldsymbol{v} + \frac{8\mu}{Z^2}\boldsymbol{v} + \rho(\boldsymbol{v}\cdot\nabla)\boldsymbol{v} + \nabla P = 0$$

Here, ∇ is the two-dimensional spatial derivative, μ is the viscosity, ρ is the density and P is the pressure. A two-dimensional unstructured mesh is generated by means of Darren Engwirda's MESH2D toolbox for MATLAB® [4]. At the nozzle inlets, refining the 5 µm mesh did not change the value of the total inflow. A gradual mesh refinement to 2 µm, however, was required in the exits channels in order to have the outflow match the inflow.

Simulations have been run for the nozzle as used for the Softhaler® and Respimat®. The viscosity of the fluid ranges from 0.25 mPa·s to 256 mPa·s, in steps of a factor 2. The density ranged from 0.125 mg/µl to 8 mg/µl, in steps of a factor two as well. While the pressure at the nozzle exits was always set to 0 bar, the pressure at the inlet was varied between 200 bar and 400 bar in steps of 50 bar.

The results of the CFD simulations are processed in MATLAB® to calculate the volume flow and energy flow at the nozzle's exits. The energy flow is divided by the volume flow to obtain the amount of kinetic energy per unit volume. This parameter is of most interest as it determines the energy available to overcome surface tension at the impingement point.

Results and discussion

The volume flow, Q, and energy per volume, E_k, for different viscosities, densities and pressures are given in Figure 1. Some data points for low viscosities are missing. In particular, these are points with high Reynolds numbers, where the Navier-Stokes equations become more non-linear. Our simulation program is optimized for water at 250 bar. Since this work focuses on high-viscosity effects, we did not re-optimise the program for higher Reynolds numbers, as doing so would incur a performance cost.

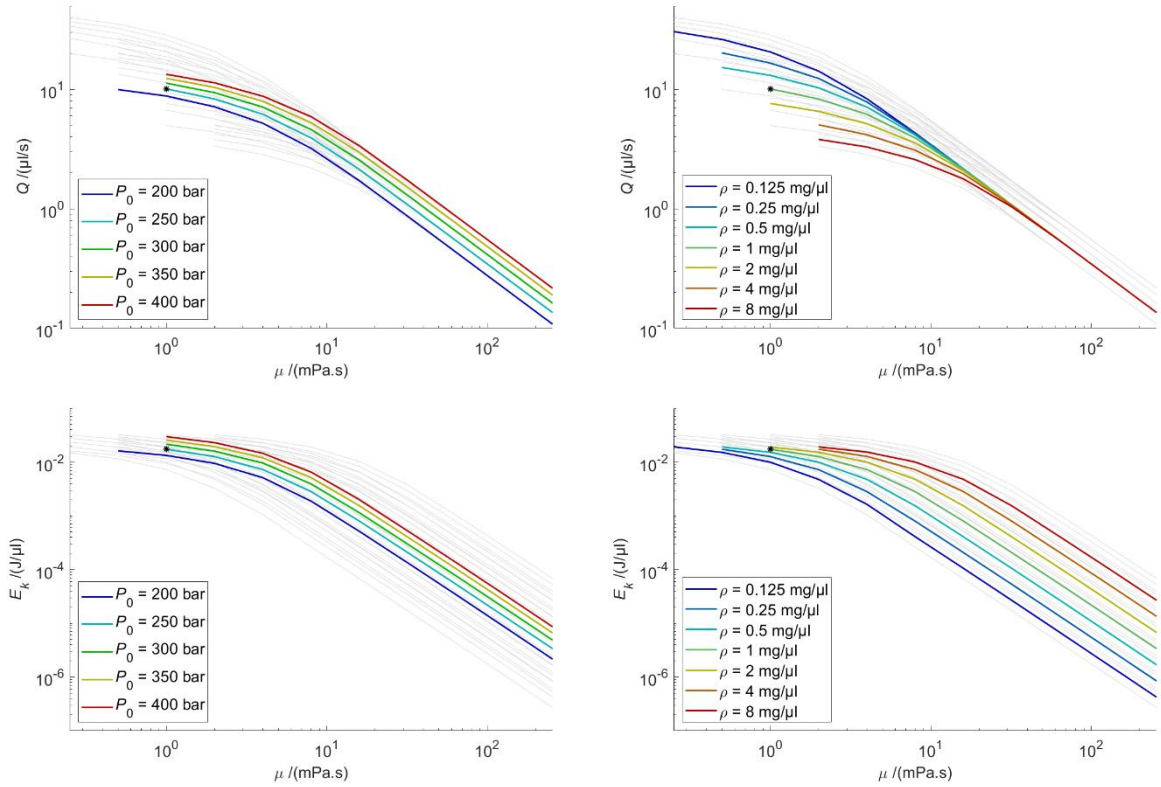

Figure 1 - Log-log-plots of the volume flow (top) and kinetic energy per volume (bottom) as function of viscosity for different pressures and densities. In the left frames, the curves for different pressures and constant density (ρ = 1 mg/ml) are highlighted. In the right frames, the curves for different densities and constant pressure (P_0 = 250 bar) are highlighted. For reference, the black * indicates water (μ = 1 mPa·s, ρ = 1 mg/ml) at the nominal pressure of 250 bar.

Although they have similar asymptotic behaviour for large viscosities, the curves in Figure 1 are hard to interpret, as there is a different curve for each pressure and density combination. It is possible to reduce the effect of density and pressure, by applying a proper scaling. The volume flow through the nozzle, Q, is the average speed at the exits, v, times the cross-sectional area of the exits, A. Assuming that the velocity at the nozzle's inlet is negligible with respect to the exits, Bernoulli's equation implies that the flow in the inviscid case, Q_{max}, is given by:

$$Q_{max} = Av = A\sqrt{\frac{2P_0}{\rho}}$$

where P_0 is the pressure at the nozzle's inlet. The viscosity on the horizontal axis can be replaced by the Reynolds number, Re:

$$Re \equiv \frac{\rho v D_H}{\mu} = D_H \frac{\sqrt{2P_0\rho}}{\mu}$$

Here D_H is the hydraulic diameter of the nozzle exits (6.6 µm) and same approximation for v in the inviscid case as above is applied. Note that the Reynolds number is inversely proportional to the viscosity. Finally, since the pressure is the potential energy at the nozzle's inlet, the kinetic energy per unit volume at the outlet is scaled with the pressure at the inlet, P_0. The scaled data is shown in Figure 2, where all curves overlap.

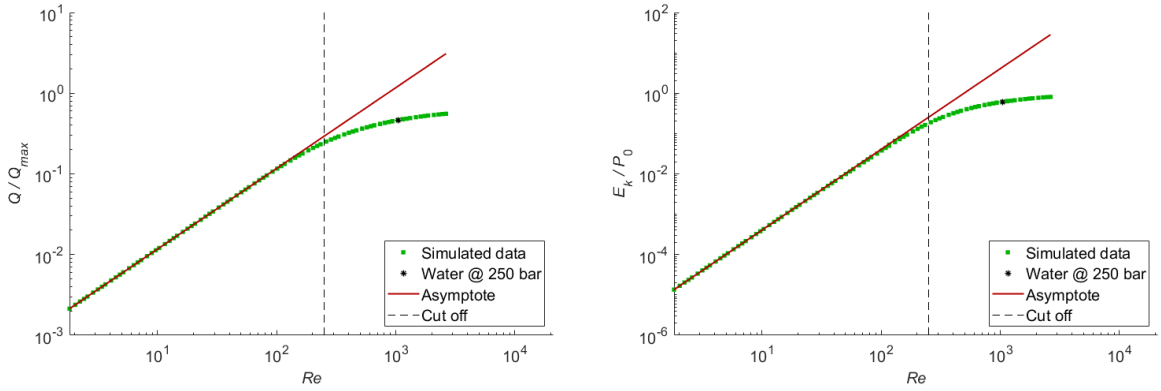

Figure 2 - Log-log-plots of the scaled flow (left) and kinetic energy (right) as a function of the Reynolds number, Re, together with their asymptotes. The black * indicates water at 250 bar, the dashed line indicates the suggested cutoff at Re = 250.

For small values of Re, the scaled flow is proportional to Re. This means that:

$$\frac{Q}{Q_{max}} \propto Re = \frac{D_H\sqrt{2P_0\rho}}{\mu} \quad \Leftrightarrow \quad Q \propto \frac{P_0}{\mu}$$

A similar relationship can be derived for the kinetic energy, since the scaled kinetic energy is proportional to Re^2 for small values of Re:

$$\frac{E_k}{P_0} \propto Re^2 = 2D_H^2\frac{P_0\rho}{\mu^2} \quad \Leftrightarrow \quad E_k \propto \rho\frac{P_0^2}{\mu^2}$$

This is not unexpected, knowing that the flow is proportional to the speed, whereas the kinetic energy is proportional to the squared speed and the density. In the asymptotic region, an increment in viscosity has to be accompanied by an equal relative increment in pressure. This may lead to a situation where the main spring force required to generate incremental higher pressures within the system leads to significant re-engineering of certain components. From the graphs in Figure 2 the asymptotic behaviour in case of the nozzle used for this research, can be estimated to set on for Re = 250, indicated by the dashed line.

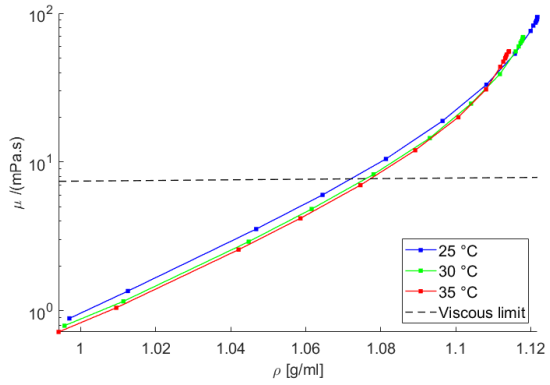

Figure 3 - Viscosity as function of density for mixtures of PEG 400 and water, with different mole fractions. [5]. Curves for different temperatures are plotted along with the viscous limit (Re = 250) calculated for 400 bar and hydraulic radius of 6.6 µm.

In order to facilitate the interpretation of this Reynolds number, we considered mixtures with different mole fractions of polyethylene glycol 400 (PEG 400) and water. Figure 3 shows the viscosity as function of the density for these mixtures as different temperatures [5]. Assuming a maximal pressure of 400 bar is feasible to be generated within the SMI, then the maximal viscosity can be calculated as function of the density. Linear interpolation on these data yields maximal mole fractions of 3.4 %, 4.1 % and 4.6 % for 25 °C, 30 °C and 35 °C respectively.

Conclusion

In this research the effects of the viscosity and density of the solvent and the pressure on the kinetic energy per unit volume of the jets have been investigated. A proper scaling has been applied where the kinetic energy relative to the applied pressure is expressed as function of the Reynolds number. For the used nozzle geometry a lower limit for the Reynolds number of 250 was found. Below this limit, the applied pressure is required to increase proportionally with the viscosity. For a mixture of PEG 400 and water this comes down to a mole fraction of 3.4 % at 25 °C. Placebo solutions with different molar fractions of PEG 400 and pressure generating main springs of increasing force profiles could provide a suitable in vitro model to validate these findings.

Essentially droplet size is of utmost importance for effective drug deposition. Further research should point out how exactly the kinetic energy influences the droplet size. In silico methods that directly estimate the droplet size [6,7], are computationally very demanding. On the other hand, the above mentioned PEG 400 in vitro model could provide a simpler approach to generating the necessary droplet size data.

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