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Scale-down modeling of the filling process for protein-based parenteral drug products

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Background

Drug manufacturing consists of a series of operations, generally referred to as formulation, filling, and finishing. First, the purified form of the drug product is formulated with selected excipients, then it is filled into vials or syringes and is ready for quality inspection, labelling and packaging. [1] Filling represents the most critical operation, in which the drug product undergoes different steps, including mixing, pumping, filtration, and final filling into vials (**Figure 1**).

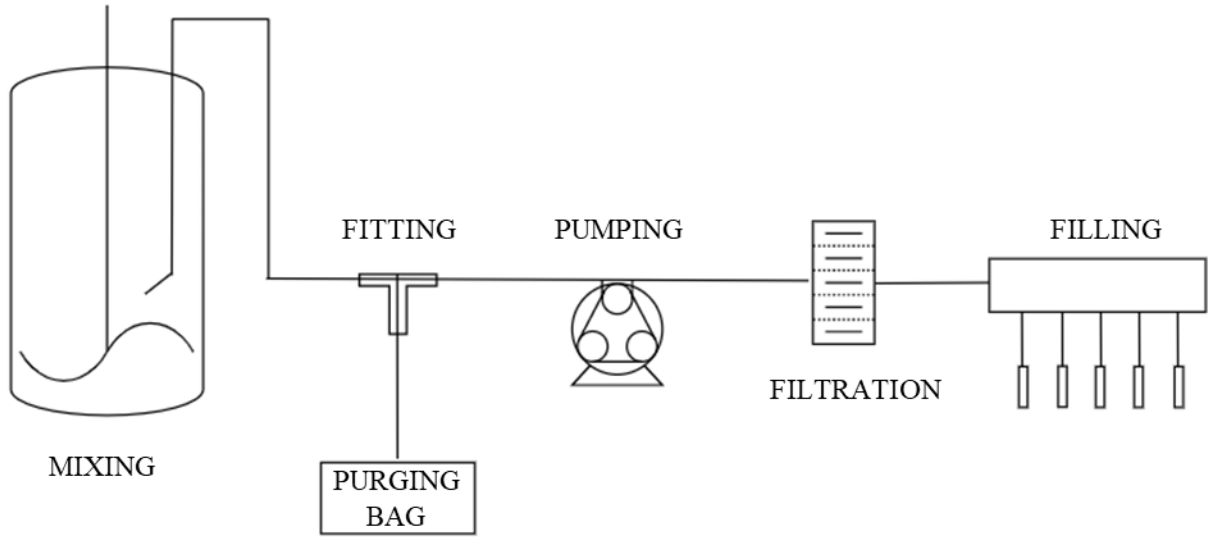

Figure 1. Typical steps in a filling line.

As protein-based parenteral drug products are intended for humans, there is concern over their stability; [2] indeed, they may be sensitive to temperature changes, oxidation, light, ionic strength and shear stress. [3] Among these, shear stress has gained interest over the past decades because of its frequent occurrence in filling lines and is the focus around which this work revolves.

Exposure of protein-based parenteral drugs to such stresses is believed to promote unfolding and subsequent aggregation, which might alter the biological activity of the drug and raise the potential for side effects. [4] Several studies conducted in recent years have tried to shed light on the actual impact of shear stress on drug products, but the presence of additional stresses (such as interfacial stress) has complicated the interpretation of the results. In this controversial landscape, it is therefore necessary to quantify shear stress in the operating units of the filling process as a first step for broader experimental investigation.

A common practice at the industrial level is the use of scale-down models to replicate the industrial line at the laboratory scale in order to perform product characterization experiments using smaller volumes of the drug products. These models result in a process design space that allows control of the Critical Quality Attributes of the drug products. Such analyses are not feasible or cost-effective at the commercial scale. Similarly, scale-up is applied to reproduce the process from the laboratory to the manufacturing unit

Two scale-down approaches are traditionally used for pharmaceutical applications. [5] One approach requires dynamic similarity (Re, *i.e.*, Reynolds number) while the other prescribes the replication in the laboratory of the worst-case scenario of the commercial line, in order to identify a safety margin.

Methods

In this project, we used Computational Fluid Dynamics (CFD) to investigate the fluid dynamics within the operating units of a filling line. CFD is experiencing significant growth in pharmaceutical applications; among other benefits, it can accelerate product and process development, as well as facilitate optimization of existing processes. [6]

The finite volume method-based open-source code OpenFoam 9 was used (https://github.com/OpenFOAM/OpenFOAM-9). The simulations were carried out on an Intel (R) Xeon (R) Gold 5118 CPU at 2.30 GHz and 128 GB of RAM. The simulations' post-processing was conducted via Python 3.8 and the Paraview application.

An incompressible and Newtonian fluid was considered to represent the drug product [7] and gravity was neglected. Steady-state simulations were implemented, rather than transient ones, since they entail a more straightforward set up and a lower computational cost.

Both laminar and turbulent flows were investigated, which both occurs in filling lines; when dealing with turbulent flows, the $k-\omega\ SST$ (Shear Stress Transport) was used to model the

turbulence in the RANS (Reynolds Averaged Navier-Stokes) framework. This model introduces some transport equations, namely for turbulent kinetic energy (k) and specific turbulent dissipation rate (ω).

For each operating unit of the filling line studied, a specific method was pursued to develop the fluid dynamic domain. Further, blockMesh and snappyHexMesh utilities were utilized to build the computational grid. Grid independence studies were conducted for each geometry to ensure the solution of the simulations remained invariant when the mesh was tightened.

In addition, when modeling the sterilizing filtration unit, experiments were performed in order to assess the filter permeability for experimental comparison with the models (**Figure 2**); in particular, the pressure drop across the filter for a specific inlet flowrate was evaluated using pressure sensors (P).

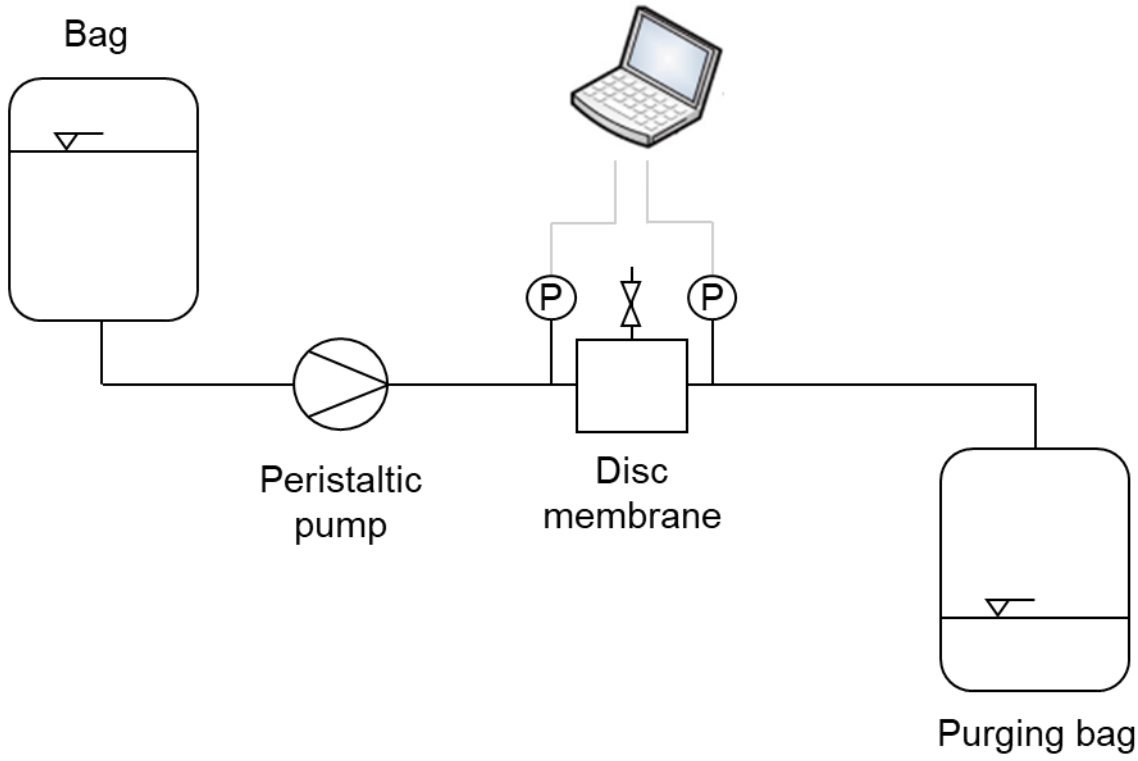

Figure 2. Experimental set up.

Results

We developed a model for calculating the shear stress distribution using a shear history-based approach. In detail, we considered a representative number of particles, *i.e.*, active molecules, within the domain and studied their history of shear stress, residence time and velocity. Based on

this information, we calculated an average shear stress. In **Figure 3** the trajectories and velocities of particles moving within typical fittings, used for sampling operations, can be seen as an example.

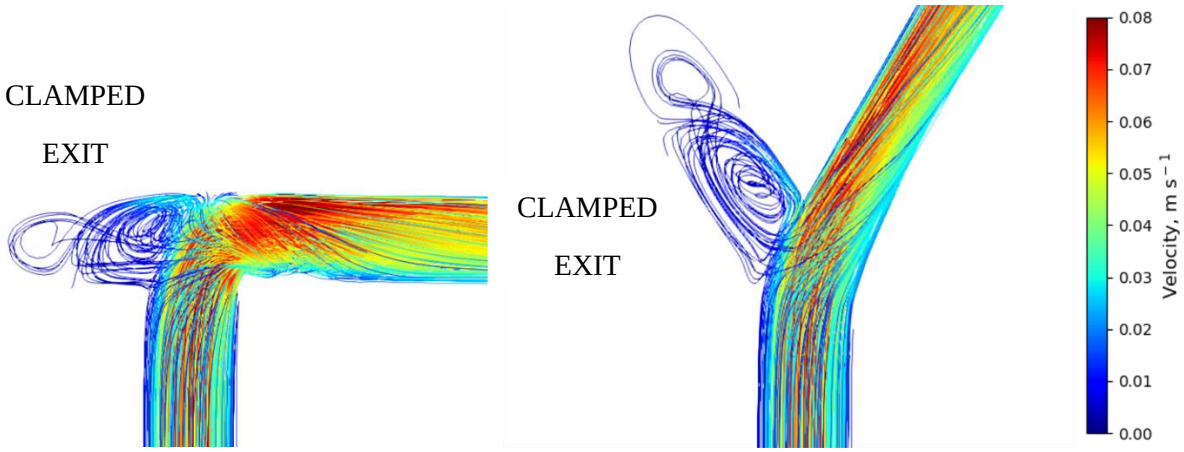

Figure 3. Particles are followed through their streamlines in T- and Y-fittings. Their trajectories (and velocities) are displayed.

This proposed shear history-based approach has been applied on different operation units of the filling line and under different fluid dynamic conditions. To provide an example, **Figure 4** displays the shear stress distribution experienced by the particles when flowing through a tubing under turbulent conditions. The fluid volumetric flowrate fraction is used to weight the shear stress contributions.

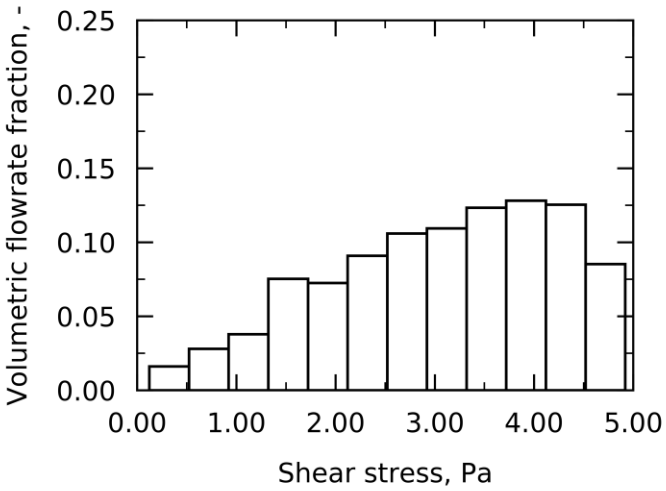

Figure 4. Shear stress distribution under turbulent conditions in a tubing.

It can be observed that the maximum shear stress, *i.e.*, around 5 Pa, is experienced only by a small portion of the entire formulation (8%), while the majority of the product is subjected to a much lower stress.

In this light, we have also developed a scale-down approach aimed to ensure representativeness between the process at industrial and laboratory scales using the shear stress distribution as a scaling parameter. In addition, we compared this approach with those traditionally used in the pharmaceutical industry and this shown to provide greater representativeness in terms of shear stress exposure.

Conclusions

This work addresses a current industrial problem, by focusing on the assessment of the exposure to shear stresses experienced by the product as it passes through some of the equipment in the filling line. In addition, the work done on scale-down approaches introduces a novelty in the pharmaceutical realm, where scale-down is never done considering the process from the product's point of view. Nonetheless, unlike other industrial processes, product quality monitoring is fundamental; thus, it is pivotal that the scale-down approach maintains the same shear stress exposure as the commercial scale, which was considered to be that resulting from shear effects.

This work can lay the groundwork for further experimental investigations to evaluate the effect of the shear stress exposure, we calculated for the various components of the line, on the stability of the parenteral drug product.

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