Impact of Shear Rate on the Flocculation State and Dissolution of Injectable Suspensions: A Numerical Study

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Abstract

Qualitative model based on fluid dynamics and discrete element method was successfully developed to predict the particle size distribution of drug suspensions under the effect of flow shear stress. Results indicate a monotonically decreasing relationship between injection rate and D_{50}.

Background

Long-acting injectables (LAI), e.g., suspended particulate, have gained significant consideration due to their convenient administration, reduced dosing frequency, as well as continuous and controlled release of active pharmaceutical ingredients (APIs). In addition, injectable suspensions are also very helpful for effective long-term management of chronic diseases. However, the prolonged duration of drug release, coupled with the relatively high amount of drug contained in one dose of an injectable suspension, may under some conditions entail higher risk, relative to an immediate release injectable. It is thus important to fully understand the formulation design and quality of injectable suspensions. The flocculation properties of injectable suspensions can influence the effective particle size of a suspension, dissolution profiles, and potentially pharmacokinetic effectiveness of the products. To understand the product performance, it is critical to investigate the impacts of injection process on the interactions between particulates, particle size distribution, and dissolution behavior (Fig. 1). This work focused on developing an improved numerical methodology to assess injectable suspension performance.

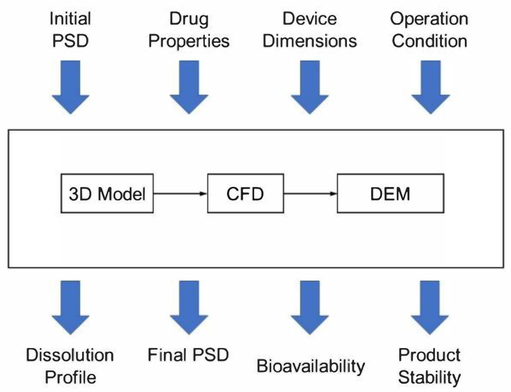

Figure 1. Graphical motive of studying suspension dissolution in injection product using simulation method

Materials and Methods

We developed a CFD-DEM model to simulate the injection process of Triamcinolone acetonide (TA) suspensions using the Hertz-Mindlin (H-M) model with the Johnson-Kendall-Roberts (JKR) cohesion model. To be specific, the 3-dimensional (3D) geometry model of the syringe and needle was constructed using computer-aided design software (e.g., ANSYS SpaceClaim). Then, the solution inside the syringe and needle was treated as a continuous phase, and the varying flow field and shear conditions were simulated by solving continuity and Navier-Stokes equations within the injection syringe. Discrete Element Method (DEM) was calibrated and coupled with CFD results to capture the aggregation and breakup of colloidal particle aggregates in shear flow (Fig. 2). Finally, the effect of shear stress on the final PSD was investigated.

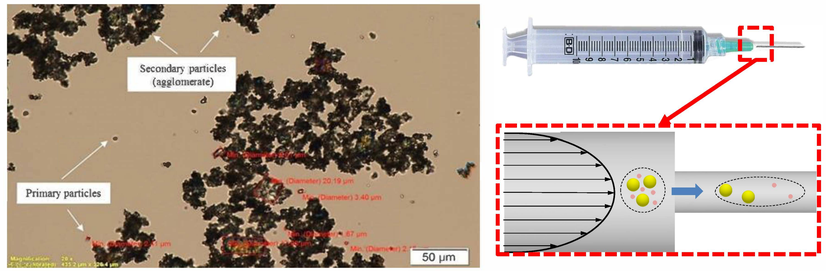

Figure 2. (Left) Polarized light micrograph (20x) of TA suspensions showing the presence of primary active pharmaceutical ingredient (API) particles (~2 µm) and secondary flocculates-agglomerates (>10 µm); (Right) modeling mechanism of TA agglomerates breakup

The H-M JKR model (Fig. 3) describes the adhesive theory using a balance between stored elastic energy (i.e., normal and tangential elastic forces) and loss of surface energy (adhesion force). We assumed that the adhesion originated from van der Waals force and electrostatic force. The rationale to choose the H-M JKR model is that the model has been proved to be able to describe the adhesion resulting from the short-range surface forces for studies of agglomeration and de-agglomeration at micro-/nano-scale.

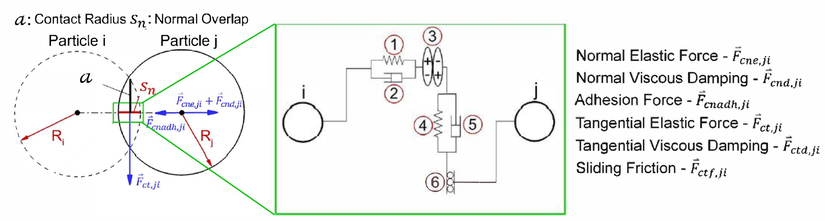

Figure 3. Particle force balance schematic with particle-particle interaction forces employed in the H-M model with JKR cohesion for DEM

Results and Discussion

For syringe with gauge 27, three injection conditions were simulated, i.e., injection flow rate (Q) at 3, 6, and 12 L/min. Figure 4 indicates the particle deagglomeration due to flow shear effect/velocity gradient at the entrance of needle. Particle size was tracked individually after exiting the needle. The PSD is illustrated in Fig. 5. The result shows that when flow rate increases from 3 to 12 L/min, the particle size shifts to smaller size with a change of 49.6% in D_{50}.

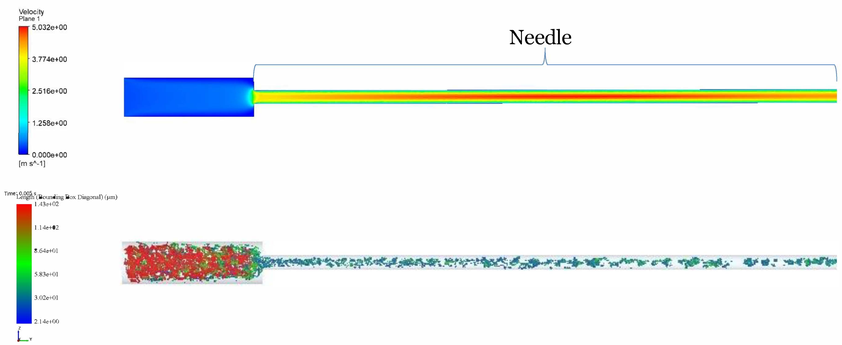

Figure 4. (Top) Velocity field on sagittal plane of syringe; (Bottom) Particle transport and interactions during injection (colored with particle size)

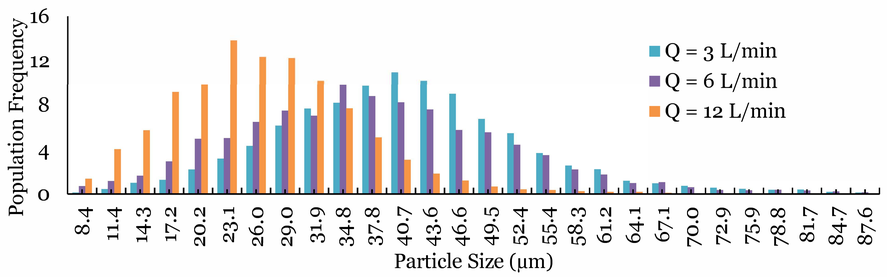

Figure 5. Particle size population frequency at Q = 3, 6, and 12 L/min

Conclusion

- A one-way coupled CFD-DEM model was established to simulate the injection process of suspended TA particulate using a syringe and predict the TA PSD after injection.
- The model predicted a change of 49.6% in D_{50} when Q increased from 3 to 12 L/min, indicating the flow velocity gradient effect on the TA suspension PSD.

Disclaimer

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