Numerical Modeling of Flocculation and Creaming of Drug Particles inside the Canister of a Metered Dose Inhaler

Emadeddin Javaheri, Reinhard Vehring, and Warren H. Finlay

Department of Mechanical Engineering, University of Alberta, Edmonton, AB, Canada

Introduction

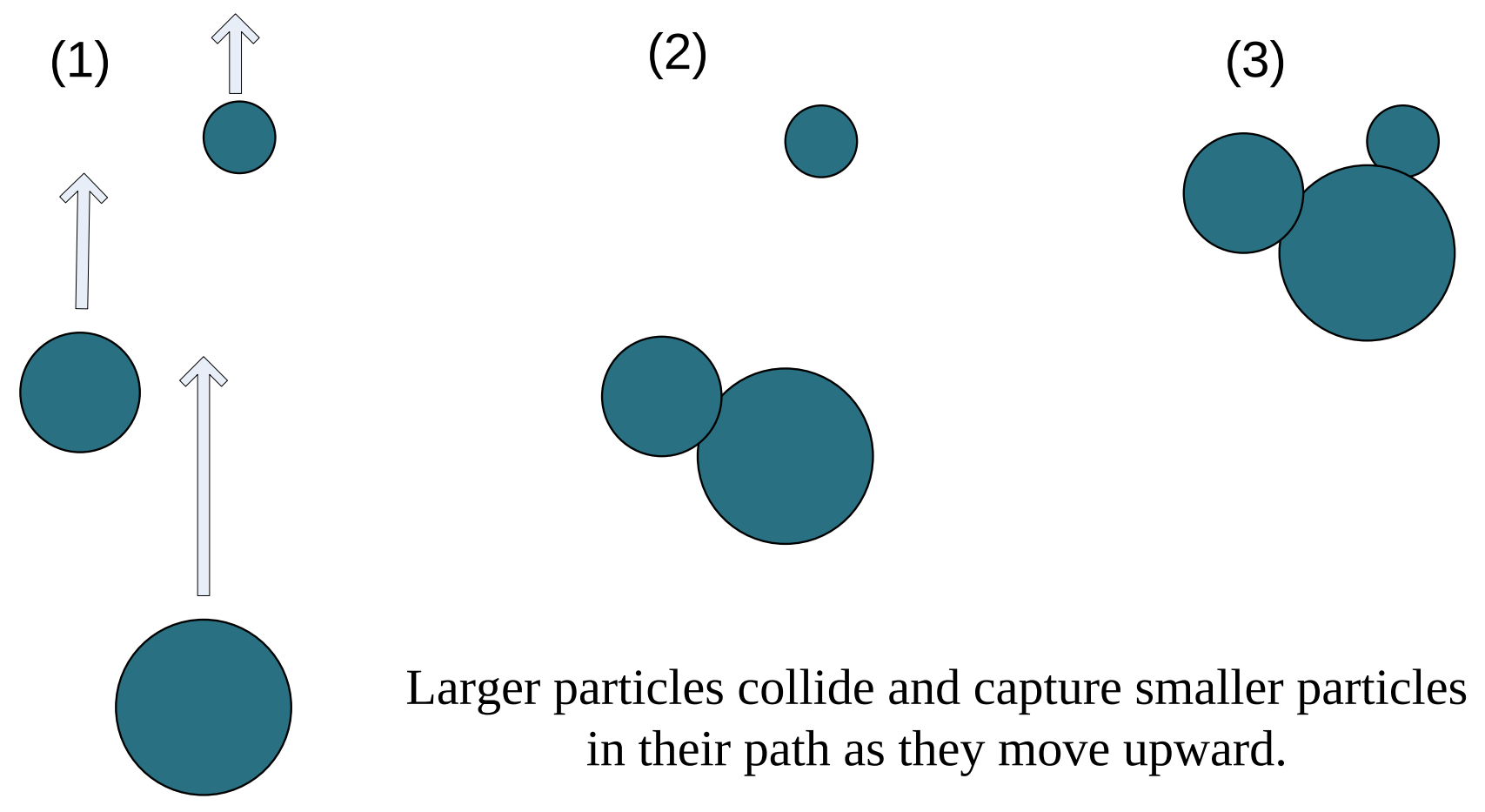
Consistent drug delivery from metered dose inhalers (MDIs) can occur only if the drug-propellant system in the canister remains stable over time. Flocculation and creaming or sedimentation of suspended drug particles can negatively impact drug dosing. The first steps towards mathematical modeling of flocculation and creaming or sedimentation in the canister are performed in this study. We assume that Brownian motion and buoyancy or gravity driven motion dominate the collision of particles and thereby flocculation. The goal is to simulate the transient upward or downward motion of the particles and predict the amount of particles which separate in the form of a cream or sediment layer.

Method

❖ All suspensions are inherently thermodynamically unstable. Through random motion over time, particles flocculate because of the natural tendency to decrease their large specific surface area and excess surface energy.

❖ The frequency of particle-particle collision depends on inter-particle forces, particle size distribution, particle concentration, dispersion medium, viscosity, and temperature.

❖ Particle collision inside the canister of an MDI is governed by Brownian motion and buoyancy. The latter also controls the gradual upward drift of the particles when the true density of the particles is lower than that of propellant.



Larger particles collide and capture smaller particles in their path as they move upward.

❖ The theory of inter-particle forces in non-aqueous media, such as an HFA propellant, is not well developed [1], so the effect of these forces is not considered in this study, but once these effects are discovered and elucidated, they could be conveniently incorporated into the collision kernels which are applied in our simulations.

❖ The dynamic formula governing the number concentration of the particles, as a function of time and position, can be written in the form:

$$\frac{\partial n_k(z,t)}{\partial t} + v_z \frac{\partial n_k(z,t)}{\partial z} = \left[\frac{\partial n_k(z,t)}{\partial t}\right]_{Flocculation}^{Brownian} + \left[\frac{\partial n_k(z,t)}{\partial t}\right]_{Flocculation}^{Buoyancy}$$

❖ The above formula is a system of nonlinear partial differential equations (PDE) in which n_k is the number concentration of the kth particle size, z is the vertical distance from the bottom of the canister, and v_z is the upward drift velocity of the particles.

❖ Flocculation due to Brownian motion and buoyancy are modeled using Smoluchowski collision theory [2,3]. The assumption of independent Brownian flocculation and buoyancy flocculation is obviously made. It was also assumed that every collision between particles leads to coalescence.

Results

❖ The system of nonlinear PDEs was solved for initially monodisperse, 1.0 μm aerodynamic diameter particles suspended in propellant HFA 227. Initial number concentration of the particles was assumed to be $10^{10}/cm^3$, corresponding to a suspension concentration of 16.6 mg/cm³. The density of the propellant is 1400 kg/m³, the true density of the particle material is 1100 kg/m³, and the density of the particles is 100 kg/m³. The propellant surface was 4 cm above the bottom of the canister. Figure 1 depicts the schematic of variations in concentration due to upward migration of the particles.

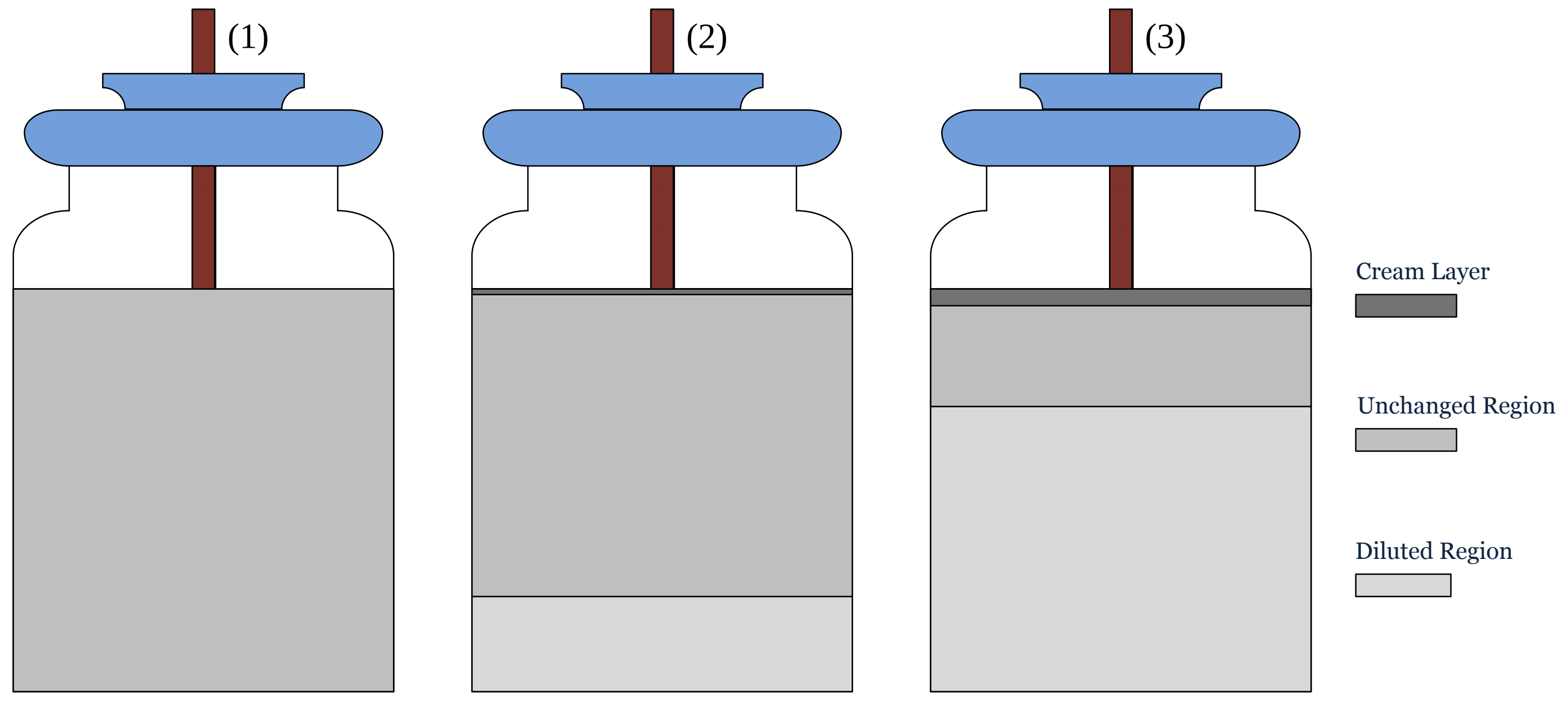


Figure 1
Schematic of variations in concentration due to upward migration of the particles

❖ Figure 2 depicts the normalized mass concentration vs. normalized height level at different times, in which normalized mass concentration is the mass concentration at a particular time and position divided by initial mass concentration at that position, and normalized height level is the height of a position divided by the height of the surface of the propellant. It should be noted that the mass concentration of the particles at the propellant surface is not reported in Figure 2.

❖ Particles gradually accumulate at the surface and form a cream layer, which is a highly concentrated layer of particles. Figure 3 depicts the percent of the total mass accumulated at the surface vs. time.

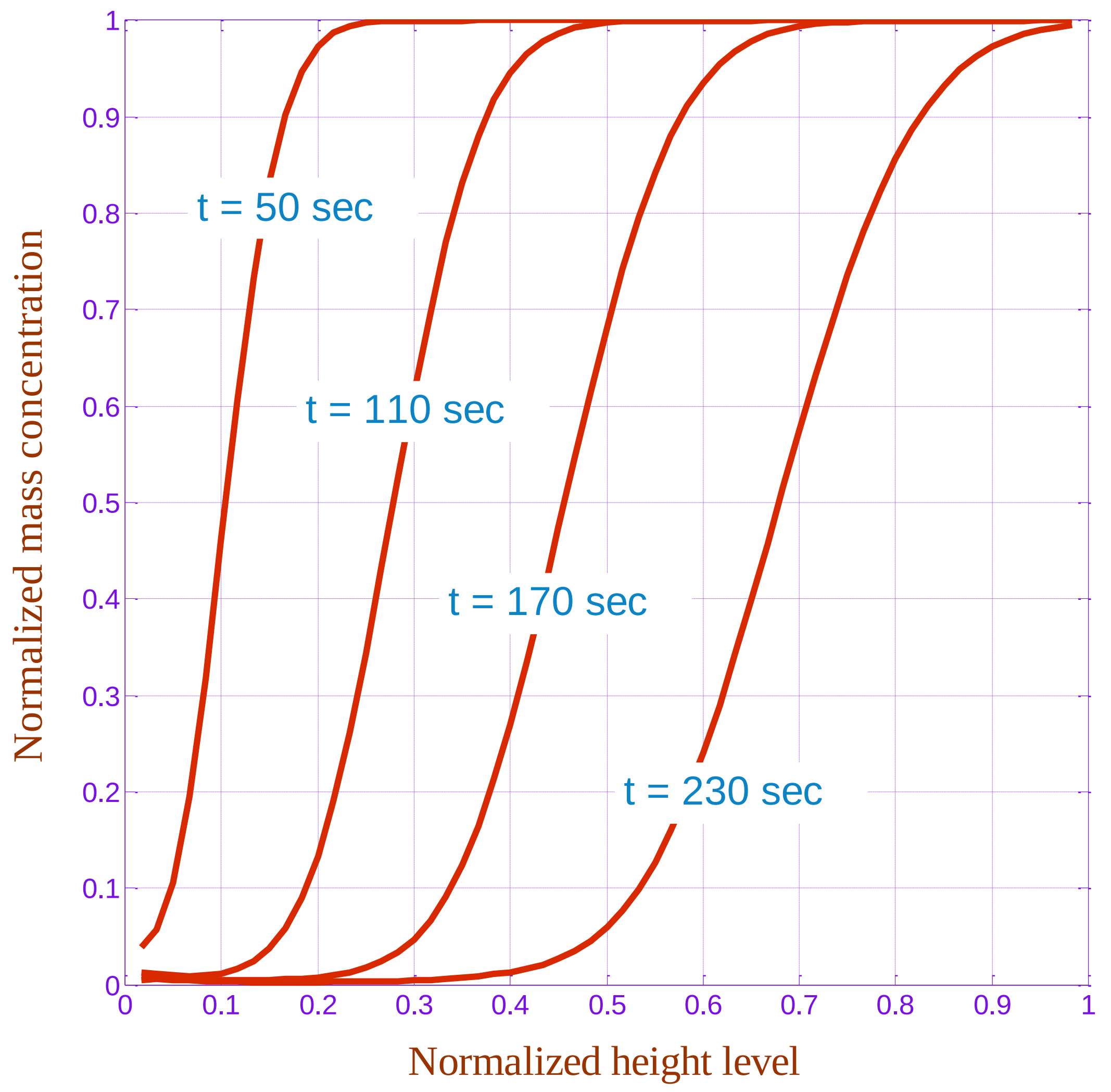


Figure 2
Normalized mass concentration vs. normalized height level over time

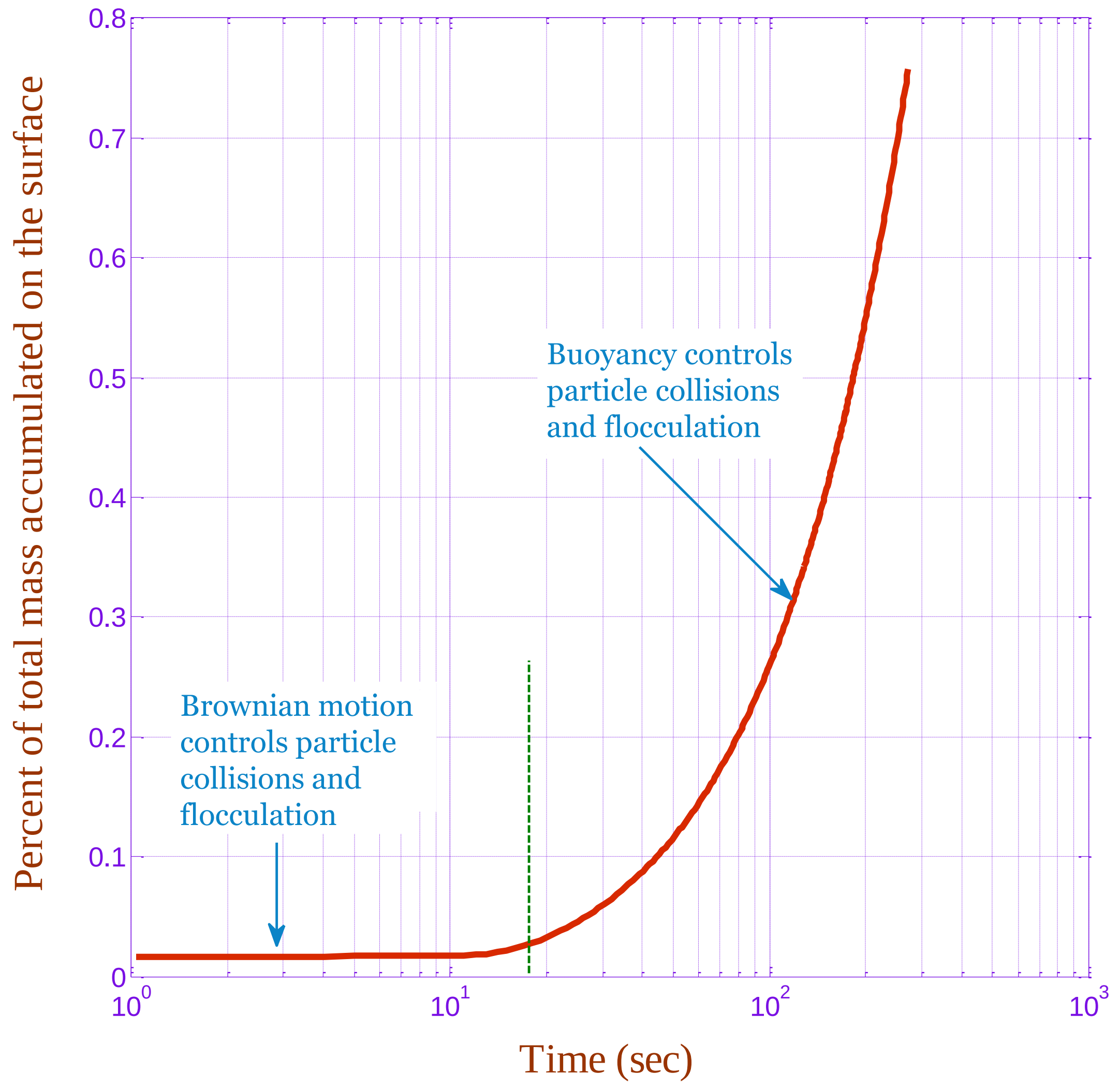


Figure 3
Percent of the total mass accumulated at the surface vs. time

Discussion and Conclusion

❖ The results capture the essential features of the simultaneous flocculation and creaming of particles inside the canister. The concentration of the particles at different heights as well as the mass fraction accumulated at the surface can be monitored over time.

❖ Figure 2 suggests that the changes in the mass concentration propagate like a wave through different heights from the bottom to the top, i.e., at each time, mass concentration reduces at lower heights but remains unchanged at upper heights.

❖ Figure 2 implies that all the particles that have migrated from lower levels accumulate at the propellant surface instead of distributing over levels below the surface.

❖ As a clarifying example, at t=110 s, mass concentrations at normalized heights higher than 0.5 are unchanged, because these upper regions have not yet received the wave of diminution.

❖ Figure 3 indicates that two different phases can be distinguished during the process: in the first phase Brownian motion controls the collision of particles and the accumulation of particles on the surface is negligible. In the second phase, larger particles collide and capture smaller particles in their path as they move upward. This phenomenon is controlled by buoyancy.

❖ Figure 3 makes obvious that the rate of accumulation of the particles on the surface is appreciably higher when collision of particles is controlled by buoyancy.

❖ The formation of the cream layer is not necessarily an indication of poor product performance, because the particulate phase which is accumulated at the surface may be re-dispersed with agitation.

❖ The present simulation approach allows examination of the flocculation and creaming of hypothetical MDI suspension formulations, which may be useful in the design and development of improved MDI formulations.

References

1. Johnson, K.A. (1996), “Interfacial Phenomena and Phase Behavior in Metered Dose Inhaler Formulations,” Lung Biology in Health and Disease (94), Inhalation Aerosols: Physical and Biological Basis for Therapy, A.J. Hickey (ed), Marcel Dekker, New York, NY, pp. 385-415.
2. Friedlander, S.K. (2000), Smoke, Dust, and Haze: Fundamentals of Aerosol Dynamics, Oxford University Press, New York, NY, pp. 196-99.
3. Williams, M.M.R. and Loyalka, S.K. (1991), Aerosol Science Theory and Practice: With Special Applications to the Nuclear Industry, Pergamon Press, Oxford, UK.