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

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## INTRODUCTION

Drug delivery from metered dose inhalers (MDIs) can occur effectively 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.

## METHODS

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. Particles collide with each other basically because of their relative motion. When the continuous phase inside the canister of an MDI is motionless, this is governed by Brownian motion and buoyancy. The latter also controls the gradual motion of the particles, which is upward when the true density of the particles is lower than that of propellant. During this process, particles flocculate and drift upward simultaneously. Particle interactions, including attractive Van der Waals forces and repulsive electrostatic and steric forces may influence the rate of collisions. Unfortunately, the theory of inter-particle forces in non-aqueous media is not well developed. Particularly, the relevance of electrostatic forces in liquids with low dielectric constants and low conductivity, like propellants, is still a point of controversy. See Johnson (1) for a short introduction to colloidal

theories applicable to propellant formulations. See also Farr *et al.* (2) for a discussion on the stabilizing effects of surfactants on suspension MDI formulations. Although inter-particle forces can affect the rate of collisions, they will not sensibly impact the trend of particle flocculation. See, e.g., Friedlander (3) for details on the effect of Van der Waals forces on Brownian coagulation. 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 equation governing the number concentration of the particles, as a function of time and position, can be written in the form:

$$\frac{\partial n_k(z,t)}{\partial t} + v_z \frac{\partial}{\partial z}\left(n_k(z,t)\right) = \left[\frac{\partial n_k(z,t)}{\partial t}\right]^{Buoyancy}_{Flocculation} + \left[\frac{\partial n_k(z,t)}{\partial t}\right]^{Brownian}_{Flocculation} \quad \textit{Equation 1}$$

Equation 1 is a system of nonlinear partial differential equations (PDE) in which $n_k$ is the number concentration of the $k^{th}$ particle size, $z$ is the vertical distance from the bottom of the canister, and $v_z$ is the upward drift velocity of the particles. The second term on the left hand side should not be misunderstood as a convection term, because the continuous phase in the suspension is motionless, so the particles are not transported by fluid flow. Flocculation due to Brownian motion is modeled using Smoluchowski collision theory. Collision kernels for buoyancy flocculation are also derived by applying ideas similar to Smoluchowski's theory. The assumption of independent Brownian flocculation and buoyancy flocculation is obviously made. Moreover, it was assumed that every collision between particles leads to coalescence. See Williams and Loyalka (4) for a detailed discussion on collision kernels for many different mechanisms with methods of combining simultaneous mechanisms.

To solve the PDE system, the first order position derivative on the left hand side was approximated by first order backward difference. 60 control volumes in the vertical direction were found to allow grid independent solutions. The time derivative was analyzed with the aid of $4^{th}/5^{th}$ order Runge-Kutta-Fehlberg method with adaptive time steps. Relative error was adjusted to vary between $10^{-3}$ and $10^{-4}$.

The system of nonlinear PDEs, Equation 1, was solved for initially mono-disperse 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/$cm^3$. The density of the propellant is 1400 kg/$m^3$, the true density of the particle material is 1100 kg/$m^3$, and the density of the particles is 100 kg/$m^3$, which are values seen with engineered particle formulations (5). The propellant surface was 4 cm above the bottom of the canister.

## RESULTS

Figure 1 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.

Particles gradually accumulate at the surface and form a cream layer, which is a highly concentrated layer of particles. Figure 2 depicts the percent of the total mass accumulated at the surface vs. time. It should be noted that 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.

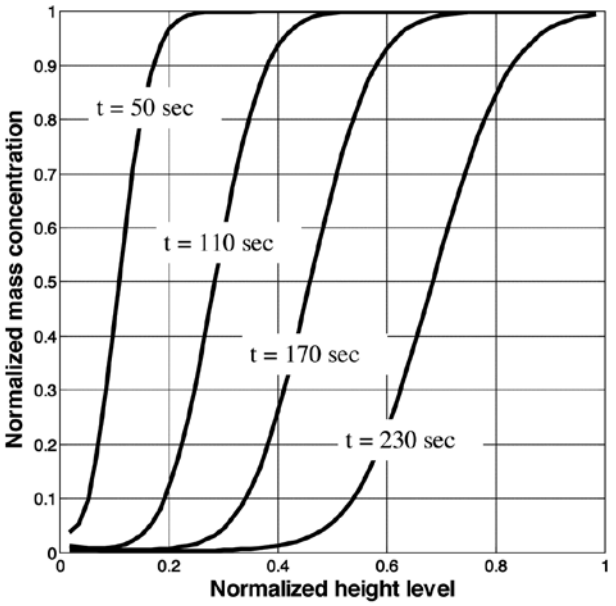


**Figure 1.** **Normalized mass concentration vs. normalized height level over time.**

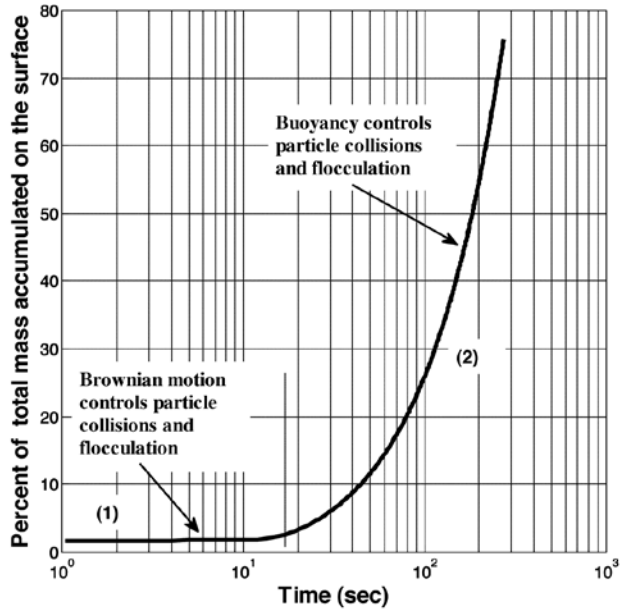


**Figure 2.** **Percent of the total mass accumulated at the surface vs. time**

## DISCUSSION AND CONCLUSIONS

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 1 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. These upper regions have not yet received the wave of diminution, e.g., at t=110 s, mass concentrations at normalized heights higher than 0.5 are unchanged. This implies that all the particles that have migrated from lower levels accumulate at the propellant surface instead of distributing over levels below the surface. It should be noted that the mass concentration of the particles at the propellant surface is not reported in Figure 1.

Figure 2 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 quite trivial. In the second phase, larger particles collide and capture smaller particles in their path as they move upward. This phenomenon is controlled by buoyancy. The rate of accumulation of the particles on the surface is appreciably higher during this second phase.

The results of this simulation help predict the changes in mass concentration of drug particles at different height levels inside the canister of an MDI. Such changes in concentration may crucially impact drug dosing. 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.

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