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Diffusion controlled formation of microparticles

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ABSTRACT

A new hybrid analytical/numerical model that describes the formation of structured microparticles from evaporating microdroplets is presented. It is applicable when diffusion and surface recession are the main mechanisms of mass transport in the droplets. The model accounts for the transient nature of the solute concentration profiles during the evaporation process and thereby extends previously published models to particle formation processes in which the droplet surface recession rate is much faster than the diffusion in the droplets, *i.e.*, in cases with large Péclet numbers. Furthermore, the model is useful when the initial concentration of solutes in the droplets is close to saturation. The model also predicts the dry particle diameter, assuming a spherical particle, particle density, and aerodynamic diameter. For hollow particles formed at large Péclet numbers the shell thickness can be approximated. The model is capable of predicting the radial distribution of the components in the final dry particle in the case of multi-component formulations. The results of the model were recast in a simple analytical form, which can be used in particle design without the need for numerical tools. Predictions of the model were found to be in good agreement with numerical and experimental results in the literature.

1. Introduction

There is a growing trend to use spray drying in the development of new pharmaceutical formulations, especially respirable dosage forms that contain proteins (Park et al., 2011; Schwendeman, 2002), vaccines (Corbanie et al., 2007; Corbanie et al., 2008; Lee et al., 1997), biomolecules (Maltesen et al., 2008), lipids (Vehring et al., 2012), poorly soluble actives (Boraey et al., 2013; Lu & Park), or nanoparticles (Nandiyanto & Okuyama, 2011; Okuyama et al., 2006), fueled by the ability of the process to produce dry particles with a wide range of desired properties in one simple manufacturing step (Nandiyanto & Okuyama, 2011). During the preliminary design of products that rely on microparticles, such as dairy products or pharmaceutical dosage forms, the ability to estimate final dried particle properties based on formulation and process parameters can ease process development. The properties and functionality of the final dried product may depend on the particle morphology, which may vary given the changes in the drying process parameters or the physiochemical properties of the formulation. In the case of a multi-component formulation, the spatial distribution of the different components is a key factor in the design of layered particles for micro-encapsulation (Schwendeman, 2002; Vehring, 2008; Wischke & Schwendeman, 2008), stabilization of biotherapeutics (Matinkhoo et al., 2011) and vaccines (Ingvarsson et al., 2013), and controlled release (Arifin et al., 2006) applications. Shell thickness and composition are responsible for controlling the drug release profiles and rates (Nie et al., 2010; Tan et al., 2005; Xu et al., 2013). Particle size and surface chemistry also play a vital role in targeted delivery applications (Champion et al., 2008).

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Particle engineering via spray drying (Vehring, 2008; Vehring et al., 2007) provides an efficient way of developing new formulations in a time and cost effective manner by exploring the mechanisms governing the particle formation process and providing an easy-to-use approach for systematic design of engineered microparticles for a wide range of applications (Chen et al., 2011; Feng et al., 2011).

The process of dry particle formation due to the evaporation of solution droplets has been extensively studied and reviewed (Vehring, 2008). Nandiyanto & Okuyama (2011) reviewed different dry particle morphologies and the corresponding manufacturing techniques. Generally, the theoretical description of evaporation processes is a challenging problem due to the many interacting physical mechanisms involved. However, many industrial applications rely on droplet evaporation using one of the various drying techniques (Nandiyanto & Okuyama, 2011) to obtain the final product (Vehring, 2008). Many particle formation models have been proposed in the literature to address this problem. In the development of analytical models (Gardner, 1965; Leong, 1987; Vehring, 2008) one must make simplifying assumptions such as a constant evaporation rate or constant material properties to arrive at a user friendly, approximate solution. Analytical models are generally easier to use and may provide a useful estimate of the final dry particle properties; however due to the restrictive assumptions imposed during their development, their accuracy and usability are limited (Vehring, 2008; Vehring et al., 2007). On the other hand, numerical models (Castillo & Munz, 2007a, 2007b; Eslamian & Ashgriz, 2007; Hubbard et al., 1975; Jayanthi et al., 1993; Vehring et al., 2007; Widiyastuti et al., 2007; Xiong & Kodas, 1993; Yu & Liao, 1998) can take into account the full range of different interacting physical mechanisms involved in the evaporation process at the expense of higher complexity. In practice, the usefulness of numerical models is also limited. Firstly, accurate material properties are often unavailable for systems of practical importance. Secondly, the iterative and exploratory nature of the design stage of microparticles makes the use of numerical models computationally demanding. Since production scale powders are generally polydisperse, numerical model results have to be obtained for every size distribution interval in a very time consuming fashion. Most useful would be a comparatively simple model that can accurately predict the final dry particle properties with an affordable computational effort.

Since the internal circulation inside a liquid droplet is induced by the shear forces on the surface of the evaporating droplet, internal circulation can be neglected for small droplet Reynolds numbers (Sirignano, 1999). Finlay showed that this condition is satisfied for small particles moving at low velocities relative to the surrounding gas. This condition is typically fulfilled for microdroplets in the size range of inhaled pharmaceutical aerosol particles (Finlay, 2001). For this reason diffusion can be assumed to be the dominant mechanism of mass transport.

During the evaporation of solution droplets, the radial concentration profiles of the solutes are controlled by two counteracting mechanisms. The first is the recession of the droplet surface, which promotes higher surface concentrations by sweeping the solute molecules (Fig. 1), while the second is the diffusion of solutes from the droplet surface towards its lower concentration core. The relative importance of these two mechanisms is described by the Péclet number, Pe_i, for component i, which depends on the ratio between the evaporation rate, κ, and solute diffusivity of each component in the liquid phase, D_i (Vehring, 2008; Vehring et al., 2007).

$$Pe_i = \frac{\kappa}{8D_i} \tag{1}$$

$$\kappa = -\frac{\mathrm{d}d^2}{\mathrm{d}t} \tag{2}$$

where d is the droplet diameter.

At the end of the evaporation process a solid particle is formed, either by crystallization or precipitation of an amorphous solid. Frequently, the formation of a shell is observed (Cruz et al., 2011; Gómez-Gaete et al., 2008; Gómez Gaete et al., 2008). Shell formation is initiated when the solute surface concentration reaches a critical value, *i.e.*, critical supersaturation for crystalline shells, or a concentration close to the solute true density for amorphous shells (Vehring, 2008).

For large Péclet numbers the effect of the surface recession velocity is more significant than solute diffusion, which results in a much higher solute concentration at the droplet surface compared to its core (Gómez-Gaete et al., 2008; Gómez Gaete et al., 2008). This effect can be quantified by the surface enrichment, which is the dimensionless ratio between the

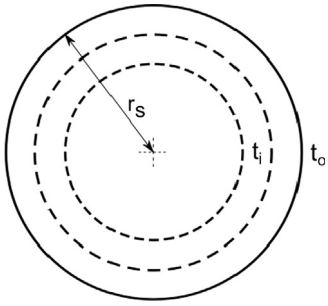

Fig. 1. The recession of the droplet surface during evaporation promotes higher surface concentration.