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Protocols

Engineering of layered, lipid-encapsulated drug nanoparticles through spray-drying

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ABSTRACT

Drug-containing nanoparticles have been synthesized through the spray-drying of submicron droplet aerosols by using matrix materials such as lipids and biopolymers. Understanding layer formation in composite nanoparticles is essential for the appropriate engineering of particle substructures. The present study developed a droplet–shrinkage model for predicting the solid-phase formation of two non-volatile solutes-stearic acid lipid and a set of drugs, by considering molecular volume and solubility. Nanoparticle formation was simulated to define the parameter space of material properties and process conditions for the formation of a layered structure with the preferential accumulation of the lipid in the outer layer. Moreover, lipid–drug demarcation diagrams representing a set of critical values of ratios of solute properties at which the two solutes precipitate simultaneously were developed. The model was validated through the preparation of stearic acid–isoniazid nanoparticles under controlled processing conditions. The developed model can guide the selection of solvents, lipids, and processing conditions such that drug loading and lipid encapsulation in composite nanoparticles are optimized.

1. Introduction

The use of nanoparticles for drug delivery offers the advantages of improved bioavailability, increased half-life, targeted delivery [1,2], and enhanced stability in biological systems [3]. Drugs can either be chemically attached or adsorbed on nanoparticle matrices or be encapsulated inside the matrices. Encapsulation of drugs in biomaterials such as polymers and lipids is advantageous because it enables multidrug (hydrophobic and hydrophilic) therapy and controlled release [4]. A thorough understanding of layer formation in composite nanoparticles, which are comprised of one or more matrix materials and drugs, is essential for the optimal engineering of particle substructures.

Composite or layered nanoparticles have recently been prepared through aerosol routes involving the controlled spray-drying of solution droplets, which in some cases involves thermochemical decomposition at high temperatures. Droplet aerosols are typically generated through shear/collision or the electrohydrodynamic breakup of liquids. The spray pyrolysis of micron-sized droplets of metal salts together with the high-temperature decomposition of the precursor has been used to produce composite metal-oxide nanoparticles [5]. Electrohydrodynamic systems, also called electrosprays, with coaxial dual- and tri-capillary geometries containing different solutions have recently been investigated for the preparation of layered, biopolymer-coated particles encapsulating multiple drugs that enable controlled drug release [6]. Air-jet atomization, which offers higher throughput rates than does electrospraying, involves the use of a single well-mixed precursor solution and has recently been used with two-solute solution precursors to prepare surface-modified nanoparticles that exhibit suspension stability [7] and to prepare drug-encapsulated nanoparticles that exhibit controlled release [8].

Particle formation through spray-drying involves the formation of solid phases in an evaporating droplet, which depends on variables such as solvent evaporation rate, process and droplet temperatures, solute solubility, molecular weight, critical supersaturation ratio, activity coefficient of the solute, and initial solute concentration. Theoretical studies have examined such particle formation to predict the particle size and structure in one-solute systems [5,9–14]. Shetty et al. [15] developed a mathematical model for the evaporation of a stationary droplet with spherical

Abbreviations: CSS, critical supersaturation solubility; FTIR, fourier transform infra-red spectroscopy; GSD, geometric standard deviation; KBr, potassium bromide; MV, molecular volume; Sc, critical supersaturation ratio; T_d, steady-state drop temperature; TEM, transmission Electron Microscopy; T_g, gas temperature.

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symmetry, wherein the evaporation rates were related to the resultant crystallinity of stearic acid nanoparticles. Bandyopadhyay et al. [16] further expanded this model to include crust formation and shell growth in order to predict the effect of variations in process conditions on final particle morphology. These two models are similar to the model developed by Messing et al. [5] as heat and mass transfer and solute diffusion processes are considered for particle formation in one-solute systems.

By contrast, in a two-solute system, in which both the process conditions and precursor properties influence layer formation examining the evaporation of precursor droplets containing two solutes is essential for identifying the conditions under which the particle formation processes lead to the formation of layered nanoparticles. Messing et al. [5] emphasized the role of differences in the solubility of precursors in governing the composition of the crust and accordingly defined the concepts of sequential and simultaneous precipitation mechanisms. Other factors that influence the formation and composition of nanoparticles include the molecular weights and initial molar concentration of the solute, process temperatures, and consequent solvent evaporation rates. A comprehensive model of a two-solute system can be used to define the parameter space of material properties and process conditions in which the process would result in the formation of layered structure, with the preferential accumulation of a desired solute in the outer layer. For widely applied systems, such as lipid-drug composite nanoparticles, such a model could help identify the operating conditions (e.g., operating temperature, solvent, and drug-lipid molar concentrations) that yield nanoparticles containing drugs encapsulated in the lipid shell.

The present study extended an existing droplet-shrinkage model [16] to include two non-volatile solutes in an atomized droplet. Specifically, the extended model was developed for stearic acid as the matrix lipid and an unspecified set of drugs (with a known molecular volume (MV) and solubility in organic solvents) as the active ingredients. The nanoparticles were prepared using a pulse-heat aerosol reactor [17]. The objectives of this study are as follows: (i) development of a two-solute diffusion model for the prediction of the particle size and composition of the outer layer, (ii) generation of lipid-drug demarcation diagrams to identify the conditions that yield lipid-encapsulated drug nanoparticles, and (iii) testing the predictive capability of the model for stearic acid (matrix lipid) and isoniazid (an antitubercular drug) nanoparticles.

2. Model description

The modeling of particle formation through the drying of submicron-scale solution aerosols containing a single solute comprises two main stages: droplet shrinkage and shell growth [16]. In the droplet-shrinkage stage, solvent evaporation is considered a coupled heat and mass transfer problem, where solvent evaporation results in evaporative cooling due to loss of latent heat along with increased solute concentration on the droplet surface. The droplet evaporation rate can be used to predict the droplet diameter as a function of time (Eq. (1)) and the change in droplet temperature with time (Eq. (2)):

$$\frac{dD_d(t)}{dt} = \left(\frac{4D_v M_v}{\rho D_d(t)}\right)\frac{P_d(t)}{RT_d(t)}F_s[K_n] \quad (1)$$

$$\frac{dT_d(t)}{dt} = \frac{12k_G}{D_d(t)^2\rho_L CP_L}\left[T_a - T_d(t) - \frac{M_v Lh_v D_v P_d(t)}{k_G RT_d(t)}\right]F_s[K_n] \quad (2)$$

where D_d (t) is the droplet diameter (m) at time t (s); F_s (K_n) is the Fuch's correction factor; $K_n = 2\lambda/D_d$ is the droplet Knudsen number with λ (m) as the mean free path of the gas; D_v ($m^2\,s^{-1}$) is the solvent vapor molecular diffusivity in air; P_d (t) is the vapor pressure (Pa) at the droplet surface; T_a and T_d (t) are ambient and drop temperatures (K), respectively; k_G is the thermal conductivity of air ($W\,m^{-1}\,K^{-1}$); Lh_v is the latent heat ($J\,kg^{-1}$) of evaporation; CP_L is the specific heat ($J\,kg^{-1}\,K^{-1}$) of the solvent; ρ_L is the solvent density ($kg\,m^{-3}$); M_v is the vapor molecular weight ($kg\,mol^{-1}$); and R ($J\,mol^{-1}\,K^{-1}$) is the universal gas constant.

Solvent evaporation is accompanied by the enrichment of the solute in the droplet, with the highest concentration occurring on the surface. The formation of a concentration gradient in the evaporating droplet results in Fick's diffusion flux, which counteracts the surface enrichment. The equation governing the concentration profile within the shrinking droplet can be considered a moving boundary problem (Eq. (3)) along with an impervious boundary condition (Eq. (4)) and a regularity condition (Eq. (5)):

$$\frac{\partial C_s(r,t)}{\partial t} = D_L\left(\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C_s}{\partial r}\right)\right), (0 < r < a) \quad (3)$$

$$\frac{-da}{dt}C_s - D_L\frac{\partial C_s}{\partial r} = 0, (r = a) \quad (4)$$

$$\frac{\partial C_s}{\partial r} = 0, (r = 0) \quad (5)$$

where C_s is the solute concentration in mole fraction; r is the radial distance from the center of the droplet diameter a (t); and D_L is the diffusivity of the solute in the droplet, calculated using the Wilke and Chang [18] equation. The solutions to these equations in various simulations were obtained through a computer program implemented in Wolfram Mathematica 9.0, wherein the droplet boundary was immobilized by scaling the radial distance (r) with the time-varying droplet radius, a (t), and transforming the equations and boundary conditions accordingly. In contrast to the more abstract and nonlinear van der Lijn transformations used in previous studies [5,11], this approach retains the basic linearity of Eq. (3).

The droplet-shrinkage stage ends when the surface-layer concentration reaches the critical supersaturation solubility (CSS) at which crust formation occurs. In earlier studies [5,11], CSS or its ratio to equilibrium solubility (i.e., critical supersaturation ratio, Sc) has often been assigned as experimentally determined constants. Because Sc values are unavailable for the multiple solute-solvent systems considered in this study, they were calculated in a generalized manner by using the criterion proposed by He et al. [19]. The time-varying drop temperature (Eq. (2)) calculated using the model reaches a constant value within a few microseconds, much before solute diffusion begins; hence, temperature-dependent parameters such as solubility and diffusivity were considered at the steady-state constant drop temperature (T_d). The steady-state drop temperatures for acetone, chloroform, ethanol, and methanol at a process temperature of 50 °C, as calculated using Eq. (2), were −1.01, 5.31, 14.46, and 5.39 °C respectively. The increase in the solute concentration on the surface layer to CSS is considered the point of crust formation, which yields the particle diameter. The subsequent shell growth regime was not modeled in the present study.

The present analysis considers a system with stearic acid as the lipid material, wherein drugs are characterized in terms of their MVs and solubility in a selected solvent. The concentration profiles of the two solutes in the droplet were modeled using separate equations (Eqs. (3)–(5)), and data on the solute solubility of stearic acid in different organic solvents, an influential parameter, were compiled from the literature [20–22] and fitted to inverse temperature to a function of the following form:

$$\ln X = q_0 + q_1\left(\frac{300}{T}\right) + q_2\left(\frac{300}{T}\right)^2 \quad (6)$$