International Journal of Heat and Mass Transfer 122 (2018) 863–876

Contents lists available at ScienceDirect

International Journal of Heat and Mass Transfer

journal homepage: www.elsevier.com/locate/ijhmt

On the particle formation in spray drying process for bio-pharmaceutical applications: Interrogating a new model via computational fluid dynamics

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ARTICLE INFO

Article history:
Received 8 December 2017
Received in revised form 10 February 2018
Accepted 12 February 2018

Keywords:
Amorphous solid dispersion
Spray drying
Computational fluid dynamics
Drying kinetics
Particle formation

ABSTRACT

Although spray drying is widely used to produce active pharmaceutical ingredients, its operation and improvement is often difficult to assess because of complex interactions between the chemical and physical properties of the solutions, and the ensuing fluid dynamic, and heat and mass transfer phenomena occurring during spray drying. Hence, computational fluid dynamics (CFD) modeling is used to provide insight into spray drying to produce pharmaceutical solid amorphous dispersions, the results of which are compared to experimental data from the modelled spray dryer during its operation. It is shown that droplets with different sizes, trajectories and breakup behaviors occur and cause droplet drying and solid powder formation differences that affect product characteristics. Based on the combined CFD and experimental information, a new drying approach is proposed and tested that is based on the precipitation of dissolved solid species and the introduction of swirl motion of the droplets during ejection from a spray nozzle. This new approach is shown to improve drying performance of difficult-to-handle pharmaceutical solutions.

1. Introduction

Spray drying is a commonly used process to produce amorphous solid dispersions of poorly water soluble active pharmaceutical ingredients (API) by dissolving the API in a volatile solvent along with polymers, surfactants and other functional excipients and then pumping the solution through an atomizing nozzle. Emanating from the atomizing nozzle are atomized droplets that are injected into a chamber with a heated processing gas; as the solvent evaporates, the dissolved species precipitate and form solid particles. Typically, these dried particles are separated and collected from the gas flow using a cyclone or electrostatic collector.

Selected spray dryer processing can help to improve bioavailability and impart the wanted time release regimen of formulations within the gastrointestinal tract; its operational parameters also control product characteristics and processing costs. For example, particle morphologies, sizes and solvent contents impact the ease with which final stage manufacturing, such as tableting and encapsulation, can be accomplished [1,2].

Experimentally, it is possible to gain some insight into spray drying by using an iterative design of experiments (DOE) procedure or a statistical treatment of process parameters and resulting product attributes. However, experimental measurements are time consuming and, typically, the number of experiments performed are insufficient to uncover all the underlying physics that would enable a predictive parametric solution to overall behavior while also optimizing the energy-consuming nature of spray drying.

Empirical procedures have also been applied to build on the fundamental understanding of spray drying, including steady-state, equilibrium-based methods applied to rate-based and CFD models [3]. Nevertheless, realistic modeling and numerical simulation results for spray drying in the presence of these oversimplified assumptions are prone to misinterpretation because the basic physics principles of the processing are not adequately satisfied.

For the modeling of particle transport and particle interactions, two types of approaches have been used, including the Euler-Lagrangian (E-L) and Euler-Euler (E-E) procedures. In E-L, the spray is considered a continuum flow of gas which contains numerous discrete droplet parcels with each parcel comprised of a group of dilute physical droplets. Then, solutions for the airflow patterns are found by calculating approximate solutions of the Navier-Stokes and

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https://doi.org/10.1016/j.ijheatmasstransfer.2018.02.043
0017-9310/

Nomenclature

A	surface area (m^2)
C	mass concentration
c_p	specific heat (J/kg K)
D	diffusion coefficient (m^2/s)
d	diameter (m)
f	drying rate retardation coefficient
H	enthalpy (J)
h	heat transfer coefficient (W/m^2 K)
k	heat conduction coefficient (W/m K)
K	rate of surface area change (m^2/s)
$\dot{M}$	drying rate (kg/s)
$\dot{m}$	mass flow rate (kg/s)
Nu	Nusselt number
Pe	Peclet number
$\dot{Q}$	heat transfer rate (W)
Re	Reynolds number
r	particle radius (m)
RH	relative humidity
Sc	Schmidt number
Sh	Sherwood number
T	temperature (K)
V	velocity (m/s)
t	time (s)
X	solution solvent content
Y	gas solvent content

Greek symbols

λ	mass transfer coefficient (m/s)
ρ	density (kg/m^3)
Υ	mass fraction of droplets of diameter greater than d

Subscripts

cr	critical
d	droplet
eq	equilibrium
g	gas phase
i	inlet
l	liquid phase
m	mean
o	outlet
s	solid phase
sr	droplet/particle surface
v	water vapor

continuity equations on a grid of control volumes. The particle phase is followed by tracking a number of individual particles through the airflow domain with the exchange or transfer of mass, energy and momentum within the continuous phase calculated along the particle trajectories. These transfer terms are applied, in turn, to the source terms of the Navier-Stokes equations of the airflow to incorporate interactions between the two phases, i.e. droplets and gas.

In the E-E approach, the airflow and droplet phases are both treated as interpenetrating, interacting continua. The governing equations for each phase are similar to the Navier–Stokes equations, with extra source terms representing the momentum equations introduced to account for the turbulent dispersion of droplets (Masi et al. [4] and Simonin et al. [5]). Although the E-E approach often renders more precise solutions, the less computationally intensive L-E approach and its wider range of applicability have made it the preferred choice for spray drying modeling [6].

To account for transfer terms in the mass, energy and momentum equations for a dispersed particulate phase within a continuous gas phase, the dynamic thermal and hydrodynamic behavior of the droplets must be known; this behavior can be generally understood to include three stages. First, at high solvent contents when droplets have a liquid surface, the drying rates will be largely controlled by mass transfer through the boundary layer surrounding each droplet. Second, as the solvent is evaporated and the drying produces a stable shell at the droplet surface, drying rates will be determined by solvent transport throughout the interior of the particle itself until the particle solvent or moisture content is reduced to an equilibrium value that is also within the drying gas medium. The third stage is when particle drying is considered to be complete, i.e. the particle has been heated to the equilibrium temperature within the dryer. Compared to the well-established theories that have described rates for the first and last stages of droplet drying, a comprehensive agreement on how to handle the second stage of drying has yet to be achieved; because solvent or moisture transport through particles is highly dependent on the material of the particles.

Theoretical models and experimentation have been used to predict and determine droplet drying kinetics. These include: (1) the characteristic drying curve (CDC) model based on semi-empirical drying curves; (2) models based on the reaction engineering approach (REA); (3) comprehensive drying models that incorporate continuity, momentum, energy, and species conservation equations; (4) deterministic models containing distributions of the solid component described by a population balance; and (5) empirical models obtained solely by regression methods to obtain the explicit time-dependent functions usable in CFD modeling. The following summarizes these models and describes some major studies in which they were used.

(1) In the CDC model, the second stage drying rate is typically determined by using a characteristic drying curve. It is assumed that at each volume-averaged free moisture content within a dryer, a corresponding specific drying rate occurs that is independent of the external drying conditions and related to the unhindered drying rate within the first stage of drying period. During the second stage, the relative drying rate has been represented as a function of a characteristic moisture content parameter which, for example, can be described to depend on the difference of vapor pressures at the liquid-gas interface (Keey [7]). This model has presented a method for investigating droplet drying kinetics and uses a set of simplified equations that have enabled fast computations.

Langrish and Kockel [8] used CFD and a linear falling-rate curve that had a drying rate linearly proportional to the free solvent content to approximate the hindered drying of milk powder and to predict particle behavior in milk spray dryers; this study concentrated on powders with particle diameters greater than ~2 mm. Adopting the same approach but with a different convex drying rate as a function of solvent content, the 2D simulation of Woo et al. [9] for skim milk on a pilot-scale dryer showed successful CFD replication of the experimental results for outlet temperatures and particle moistures. The use of CDC has also been extensive for simulating counter-current spray dryers in the detergent industry [10–13]; and Wawrzyniak et al. [12].

(2) The REA model was introduced by Chen and Xie [14]. It uses an empirical correlation between particle solvent content and partial vapor pressure at the particle surface to estimate