Journal of Colloid and Interface Science 500 (2017) 172–181

Contents lists available at ScienceDirect

Journal of Colloid and Interface Science

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

Regular Article

Estimation of critical supersaturation solubility ratio for predicting diameters of dry particles prepared by air-jet atomization of solutions

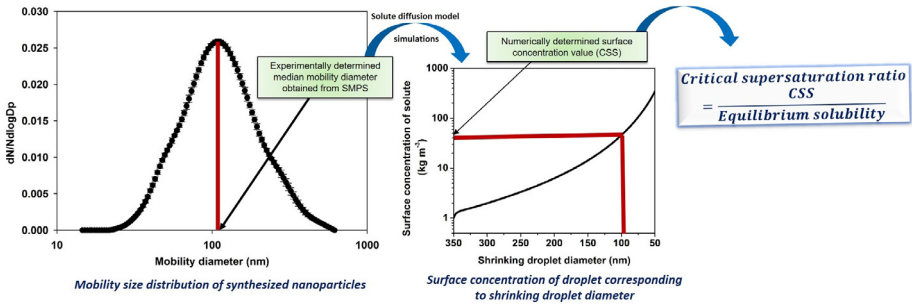
Mahak Sapra [a], Suraj Ugrani [b], Y.S. Mayya [b,*], Chandra Venkataraman [a,b]

[a] Centre for Research in Nanotechnology and Science, Indian Institute of Technology Bombay, Powai, Mumbai, Maharashtra 400076, India
[b] Department of Chemical Engineering, Indian Institute of Technology Bombay, Powai, Mumbai, Maharashtra 400076, India

HIGHLIGHTS

- Crust formation issue in particle size prediction modeling in spray drying.
- Hybrid technique for estimation of critical supersaturation ratio.
- New evidences on changing droplet diameter, induction time lag and interfacial tension.
- Validation and application for engineering nanoparticle size.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 10 January 2017
Revised 1 April 2017
Accepted 4 April 2017
Available online 6 April 2017

Keywords:
Equilibrium solubility
Droplet evaporation
Droplet diameter
Solute diffusion model
Concentration dependence
Interfacial tension
Induction time

ABSTRACT

Air-jet atomization of solution into droplets followed by controlled drying is increasingly being used for producing nanoparticles for drug delivery applications. Nanoparticle size is an important parameter that influences the stability, bioavailability and efficacy of the drug. In air-jet atomization technique, dry particle diameters are generally predicted by using solute diffusion models involving the key concept of critical supersaturation solubility ratio (Sc) that dictates the point of crust formation within the droplet. As no reliable method exists to determine this quantity, the present study proposes an aerosol based method to determine Sc for a given solute-solvent system and process conditions. The feasibility has been demonstrated by conducting experiments for stearic acid in ethanol and chloroform as well as for antitubercular drug isoniazid in ethanol. Sc values were estimated by combining the experimentally observed particle and droplet diameters with simulations from a solute diffusion model. Important findings of the study were: (i) the measured droplet diameters systematically decreased with increasing precursor concentration (ii) estimated Sc values were 9.3 ± 0.7, 13.3 ± 2.4 and 18 ± 0.8 for stearic acid in chloroform, stearic acid and isoniazid in ethanol respectively (iii) experimental results pointed at the correct interfacial tension pre-factor to be used in theoretical estimates of Sc and (iv) results showed a consistent evidence for the existence of induction time delay between the attainment of theoretical Sc and crust formation. The proposed approach has been validated by testing its predictive power for a challenge concentration against experimental data. The study not only advances spray-drying technique by establishing an aerosol based approach to determine Sc, but also throws considerable light on the interfacial processes responsible for solid-phase formation in a rapidly supersaturating system. Until satisfactory

Abbreviations: CMD, count median mobility diameter; CSS, critical supersaturation solubility; ES, equilibrium solubility; GSD, geometric standard deviation; SA, stearic acid; Sc, critical supersaturation solubility ratio; T_d, steady-state drop temperature; T_g, gas temperature.

* Corresponding author.
E-mail address: ysmayya@iitb.ac.in (Y.S. Mayya).

http://dx.doi.org/10.1016/j.jcis.2017.04.008

theoretical formulae for predicting CSS are developed, the present approach appears to offer the best option for engineering nanoparticle size through solute diffusion models.

1. Introduction

Air-jet atomization of precursor solution followed by controlled droplet drying has been extensively used for preparing dry powders of micro particles, for various applications in food and agricultural industry. As a simple, single-step process, it is being increasingly explored in recent times for preparing nanoparticles for drug delivery applications. It has been used for producing bio-polymeric or lipid nanoparticles with controlled size, crystallinity and surface properties [1–7]. Among these properties, nanoparticle size plays a crucial role in determining its suitability for drug delivery applications [8], making it important to be able to predict particle size for the given precursor concentration and process conditions.

Engineering nanoparticles for applications such as controlled drug release requires mathematical modeling of particle synthesis processes, for which material properties must be estimated [9]. Drying of solution droplets is a complex process which involves droplet evaporation, and the formation of solid phases governed by rate of solute diffusion, nucleation, crust formation, shell growth and drying of liquid inside the crust. These processes have been examined in a number of theoretical studies and numerical models from the point of view of predicting particle size and structure [4,10–15]. As solvent molecules evaporate from atomized droplets, solute molecules are left behind at the surface of the drop, leading to solute concentration profile, with lowest value at the center and the highest at the surface layer of the drop. Once the surface concentration of solute molecules reaches a certain critical value well above their equilibrium solubility (ES), their nucleation rate increases phenomenally, leading to the rapid precipitation and consequent formation of a solid crust [10]. This critical surface concentration is commonly referred to as the critical supersaturation solubility (CSS) and is expressed alternatively as critical supersaturation ratio (Sc) = CSS/ES [16]. The crust is assumed to be rigid enough to resist further shrinkage of the droplet and subsequent drying takes place through pores in the crust. For all practical purposes the crustal diameter is regarded as the final particle size [17]. Thus, the value of CSS or Sc plays a critical role in the predictive modeling of particle size for nanoparticles prepared by drying of solution droplets.

The concept of CSS for characterizing the appearance of solid phases during droplet drying was first proposed by Charlesworth and Marshall [18] for millimeter sized air-borne droplets. While the modeling of slurries and high concentration solute systems invoke either glass transition temperatures [19] or critical solid-fractions [20] as solidification criteria, the use of CSS is essential for sparingly soluble systems. Considering this, several mathematical models have been advanced involving this concept to understand the conversion of solution droplets to particles [10–15,17,21–23]. Few studies dealing with the formation of zirconium hydrochloride (ZHC) used an empirically determined value of Sc (1.4) in their models [12,22]. However, in certain models of micro-particle formation, Sc has been taken as unity i.e. ES itself taken as CSS [4,13,15]. The extent by which Sc exceeds unity depends upon the solute-solvent interfacial tension; higher interfacial tension [24] gives rise to larger nucleation barrier and greater value of Sc and vice versa. In general, materials with lower solubility have higher interfacial tension and hence larger values of Sc ($Sc \gg 1$) [25]. Thus, for sparingly soluble systems such as the case of lipids in organic solvents, nucleation barrier is high and Sc is expected to be well above unity. It is then crucial to determine these values for lipid/drug formulations using organic solvents. Apart from this, the concept of CSS (or Sc) is important in a fundamental way as it captures the intricate relationship between the solubility, interfacial tension and solid phase formation.

Despite being the workhorse concept of modeling droplet to particle conversion process, there exist only a few studies which either provide values of Sc or suggest methods to estimate CSS for a given solute-solvent combinations [16,21,26]. The earliest criterion for determining Sc was proposed by Melia [16] which stated that Sc is the saturation ratio at which a specified nucleation rate (one nuclei s^{-1} cm^{-3}) has been attained. This criterion was improved by Leong [21] who proposed that for an evaporating droplet, Sc corresponds to the value of surface solute concentration at which cumulated nucleation rate yields at least one critical nuclei within the droplet. Although reasonable from the nucleation theory point of view, it is computationally difficult to carry out the integration of the nucleation rate in a rapidly shrinking evaporating droplet system. A simpler criterion for Sc determination was proposed by He et al. [26] that combined experimental results with classical nucleation theory. This criterion takes into account solute-solvent properties such as molecular volume, equilibrium solubility and interfacial tension through the nucleation theoretic parameters. There is however significant empirical element in this criterion in terms of the formulae for the nucleation parameters as well as the choice of pre-factor. Also, experiments were restricted to evaporation of aqueous micro-drops, so the applicability of the criterion to rapidly evaporating nano-drops of organic solute-solvent systems requires justification.

A need for the experimental determination of Sc also stems from the concept of induction time introduced by Eslamian et al. [10,11], to account for the delay in the formation of rigid crust after the attainment of CSS. These authors suggested that actual particle diameters would be smaller than that predicted by running the solute diffusion models until the theoretical value, Sc_{th} is attained. In order to match the observed particle diameter, the model was run for further amount of time equal to the induction time at which the solute concentration would reach a new value (Sc_{expt}) i.e. $Sc_{expt} > Sc_{th}$. Although it is difficult to estimate the induction time a priori, this concept emphasizes the point that the measured Sc values cannot be lower than the theoretically estimated values. This is an important aspect to be kept in mind while comparing the theoretical Sc values against the experimental data.

The practical requirements and conceptual issues mentioned above in the context of particle engineering using spray-drying technology point at a definite need to develop experimental techniques to determine Sc. The present study addresses this question directly by proposing a method to determine Sc values for the formation of nanoparticles of lipid and drug materials in organic solvents. The method consists of experimental determination of dry particle and droplet diameters combined with numerical simulations using a droplet evaporation solute diffusion model [17] implemented in Wolfram Mathematica 9.0. The solute-solvent systems considered were stearic acid (SA) in ethanol, SA in chloroform and anti-tubercular drug isoniazid in ethanol. The study was conducted over a wide range of precursor solute concentrations