Mechanistic Formulation Design of Spray-Dried Powders†

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Abstract
Spray drying is gaining traction in the pharmaceutical industry as one of the processing methods of choice for the manufacture of solid dosage forms intended for pulmonary, oral, and parenteral delivery. This process is particularly advantageous because of its ability to produce engineered particles with improved efficacy and stability by combining active pharmaceutical ingredients or biologics with appropriate excipients. Moreover, due to its high throughput, continuous operation, and ability to produce thermostable solid powders, spray drying can be a manufacturing method of choice in the production of drugs and other formulations, including vaccines, for global distribution. Formulation design based on a mechanistic understanding of the different phenomena that occur during the spray drying of powders is complicated and can therefore make the use of available particle formation models difficult for the practitioner. This review aims to provide step-by-step guidance accompanied by critical background information for the successful formulation design of spray-dried microparticles. These include discussion of the tools needed to estimate the surface concentration of each solute during droplet drying, their times and modes of solidification, and the amount of glass stabilizers and shell formers required to produce stable and dispersible powders.

Keywords: spray drying, powders, formulation design, particle formation, pharmaceutical particles, pulmonary delivery

1. Introduction
Among the different industrial methods employed in the manufacture of pharmaceutical powders and solid dosage forms, spray drying has attracted considerable interest as a fast, scalable, and continuous process (Baumann et al., 2021; Carrigy and Vehring, 2019). By readily allowing a formulator to control or predict many of the physical properties of particles such as size distribution, density, solid-state, and radial spread of different components inside the particle, spray drying offers significant advantages over milling, the current industrial processing method of choice for the large-scale production of microparticles (Alhajj et al., 2021). The importance of glass-stabilized spray-dried products has also gained increasing appreciation due to the growing demand for thermostable platforms containing vaccines or other biologics in the battle against global pandemics and infectious diseases (Capua and Giaquinto, 2021; Gomez and Vehring, 2022; Kristensen et al., 2016). Moreover, spray-dried powders containing low-water-soluble therapeutics show improved bioavailability due to their usually achieved amorphous state as compared with the crystalline state of the raw material, especially when formulated in the form of amorphous solid dispersions (Davis and Walker, 2018; Huang et al., 2016; Ma and Williams, 2019).

In addition to the aforementioned pharmaceutical applications, spray drying was originally invented for and is still widely employed in the food industry to produce powder products such as dried milk, instant coffee, and encapsulated food ingredients (Woo, 2019). Such powders have increased shelf life, maintain flavor, and expedite global food distribution (Mohammed et al., 2020).

The process of spray drying, as shown schematically in Fig. 1, begins with the atomization of a liquid feed solution or suspension into a fine spray in a drying chamber, where it is then subjected to a large quantity of a hot drying gas made up of either nitrogen or dry air, depending on the solvent. The liquid spray is consequently rapidly evaporated, leaving behind solid particles that are then separated from the gas flow, most commonly through cyclonic separation (Pinto et al., 2021). Through evaporative cooling, the atomized droplets maintain a relatively low temperature for most of their drying history, making this process ideal for the production of temperature-sensitive powders (Ordoubadi et al., 2019).

Through a mechanistic understanding of the diverse phenomena that occur during spray drying, a particle engineer can design process and formulation parameters to meet a set of predefined production objectives and goals.
Spray drying process conditions, including inlet and outlet temperatures, drying gas flow rate, feed flow rate, and atomizing pressure, predominantly influence the size distribution of the particles, the outlet conditions of the dryer, and the production yield (Carrigy and Vehring, 2019), while spray drying formulation parameters, including total feed concentrations, choice of excipients, and feed composition, influence properties such as the radial distribution of each material inside the dried particles, their physicochemical properties, and their general morphology (Alhajj et al., 2021). Hence, careful design of both the process and formulation parameters can significantly reduce the initial research and development stage of product development, thereby decreasing production time, costs, and associated risks (Boraey and Vehring, 2014; Vehring, 2008; Vehring et al., 2007).

Many studies have succeeded in developing particle formation models (Boraey and Vehring, 2014; Ivey and Vehring, 2010; Ordoubadi et al., 2019; 2021a; 2021b) and process models (Carrigy and Vehring, 2019) that can be used during the formulation design of spray-dried powders. These models are frequently not easily accessible as their use requires knowledge of different branches of science and engineering, including mechanical, chemical, and materials engineering. In this study, we aim to reduce these challenges by reviewing the different stages of the design of engineered spray-dried particles and providing sufficient background information to make this process accessible to a broader group of scientists and researchers.

2. Formulation and process design

Like most design problems, the design of spray-dried microparticles is an iterative process. During each iteration, the formulation and process parameters are selected based on particle formation models or previous experience. This includes the estimation of the surface concentration of each component and the specific moment during the evaporation process at which they solidify. Using these data, the next logical step in the formulation design is choosing the total solids concentration and feed fractions of the active pharmaceutical ingredients (APIs), biologics, and excipients to meet the design objectives based on other factors such as the required drug loading, producibility, stability considerations, and regulatory matters. For example, the feed fractions of a shell-forming excipient and a glass stabilizer can be selected so that the former solidifies first and the latter increases the glass transition temperature above the required limit. Afterward, sample batches are spray dried and characterized to assess their performance. In case of unsatisfactory properties, the formulation and process parameters are modified until the requirements are satisfied. The different stages of such a proposed design process are shown in Fig. 2.

2.1 The choice of the solvent system

One of the first problems a formulator faces in the product development of spray-dried pharmaceutical powders is the question of which solvent system to use. Depending on solubility constraints, the answer can be as straightforward as plain water or as complicated as a multi-solvent system with correct solvent ratios. For the spray drying of biologics and APIs with adequate aqueous solubility, water is the solvent of choice because it is safe, inexpensive, and requires no capture of the evaporated water vapor at the exhaust (Davis and Walker, 2018; Selvamuthukumaran, 2019). However, more than 60% of newly discovered chemical entities and 40% of currently marketed drugs exhibit poor water solubility (Davis and Walker, 2018; Paredes et al., 2021). Hence, it is inevitable that a particle engineer will face the task of formulating a spray-dried platform for a hydrophobic active, especially when striving for significant enhancement in bioavailability after spray drying into an amorphous powder (Ojarinta et al., 2017; Salama, 2020). For such compounds, an organic solvent or a mixture of cosolvents can be selected after a thorough solubility screening. Solubility limitations are of significance only when the API is intended to be dissolved in the feed liquid, as opposed to applications in which one or more of the components are emulsified or dispersed, in which case there should be negligible solubility of the suspended material to avoid instability in the feedstock during manufacturing (Gomez et al., 2021a; Maniyar and Kokare, 2019; Wang H. et al., 2022). A handful of organic solvents have been considered as solvents or cosolvents for feed preparation, with only a limited number of these deemed safe for inhaled product development. The solvents most encountered in the literature are water, acetone, ethanol, methanol, ethyl acetate, dichloromethane, and tetrahydrofuran (Shepard et al., 2020; Vasconcelos et al., 2016).

Formulation design becomes most complicated when the solubility of the active ingredient is not high enough.
in a single solvent system and is instead higher at specific fractions in a multi-solvent system, or when the compound has a high solubility in a specific solvent but is not stable or dispersible on its own and therefore requires to be spray dried in conjunction with appropriate excipients that are soluble in another solvent, for example, budesonide, with its higher solubility in ethanol, and leucine, with its greater solubility in water (Boraey et al., 2013). For such cases, as shown schematically in Fig. 3, specific alterations can be made to the formulation or process design; for example, a cosolvent system can be used during feed preparation (Alhajj et al., 2021; Boraey et al., 2013; Mishra et al., 2018), or a 3-fluid atomizer can be incorporated (Focaroli et al., 2020; Kauppinen et al., 2018; Shetty et al., 2020; Sunderland et al., 2015).

For cosolvent systems, solubility data can be used in conjunction with advanced particle formation models to choose the optimal solvent ratios. It has previously been shown that, due to non-ideal vapor-liquid equilibria, multi-solvent droplets might have an azeotrope-like state during evaporation at which no change in the solvent composition can occur (Bader et al., 2013; Ordoubadi et al., 2019). For example, it was found that a microdroplet composed of 24 % w/w water and 76 % w/w ethanol evaporating in dry air at different temperatures, maintains a constant evaporation rate and droplet composition (Ordoubadi et al., 2019). When the ethanol content is increased (above 76 % w/w) during evaporation, the droplets will lose their water content first (ethanol enrichment), but when the ethanol content is reduced (below 76 % w/w) they will lose their ethanol content first (water enrichment). A formulator should be aware of such reversals in the drying behavior because, for example, they might cause the sensitive active to precipitate first on the surface of the droplet instead of the intended shell former.
2.2 The choice of excipients

Upon spray drying, most APIs and biologics are dried into an amorphous solid (Baumann et al., 2021; Chang et al., 2020; Chiu and Langrish, 2007). Amorphous spray-dried powders can be hygroscopic (Li L. et al., 2016; Momin et al., 2018), show poor long-term stability due to the possibility of recrystallization (Singh and Van den Mooter, 2016), and exhibit low glass transition temperatures (Červinka and Fulem, 2021). They can also be cohesive, resulting in poor powder and aerosol performance (Alhajj et al., 2021; Jüptner and Scherlieb, 2019). Furthermore, some of these adverse properties can exacerbate the others, as in the case of plasticization due to moisture uptake. To overcome these problems, biologically inert compounds or excipients can be formulated with active ingredients to act as carriers, bulking agents, buffers, dispersibility enhancers, and glass stabilizers (Lechuga-Ballesteros et al., 2019; Weers and Miller, 2015). Two such excipients frequently used for pulmonary applications and having the most impact on the particle formation process, i.e. glass stabilizers and shell formers, are discussed in detail next.

2.2.1 Glass stabilizers

Amorphous materials are in a metastable thermodynamic state and may eventually crystallize due to their microscopic molecular mobility (Kawakami, 2019; Singh and Van den Mooter, 2016). For spray-dried powders, the rate of this transition depends on the residual solvent content, ambient humidity, and storage temperature (Chiu and Langrish, 2007). It has previously been shown that storing pharmaceutical glasses at about 50 °C below their glass transition temperature prevents significant molecular mobility during their lifetime (Hancock et al., 1995). This approach has been used to design and assess spray-dried platforms containing different pharmaceutical ingredients and biological entities (Chan and Chang, 2021; Hoe et al., 2014; Shepard et al., 2021). Accordingly, for a powder product to be room-temperature-stable (assuming a storage temperature of 25 °C), its glass transition temperature, \( T_g \), needs to be more than 75 °C. The climate of the product’s intended market should also be considered. For example, for global health applications such as vaccine development for the developing and least developed countries more stringent conditions need to be accounted for (WHO Expert Committee on Biological Standardization, 2016). Hence, during formulation design, the particle engineer can aim for a predicted glass transition temperature so that \( T_g > T_{st} + 50 \text{ K} \), where \( T_{st} \) is the storage temperature. If the glass transition temperature of the amorphous drug is less than this value, then a glass stabilizer is required in the formulation to improve the thermostability of the product. A number of saccharides and polymers such as trehalose, sucrose, pullulan, and inulin are some of the glass formers that have been studied for the stabilization of spray-dried products (Carriaga et al., 2019c; Gomez and Vehring, 2022; Weers and Miller, 2015).

The prediction of the glass transition temperature is complicated since spray-dried powders may contain residual solvent that can act as a plasticizer (Patel et al., 2015; Shepard et al., 2020). The amount of the residual solvent itself is a function of the solvent-uptake properties of the powder, the outlet vapor activity (relative humidity in the case of aqueous systems), and the outlet temperature of the dryer (Carriaga and Vehring, 2019). Hence, to determine the required mass fraction of the glass-forming excipient, \( \gamma_{exp} \), the amount of residual solvent can be neglected initially and the Fox equation (Fox, 1956) can be rearranged to give

\[
1 > \gamma_{exp} > \frac{T_{g,act} - T_{g,exp}}{T_{g,act} - T_{g,act} + 50 \text{ K}}
\]

where, \( T_{act} \), \( T_{g,act} \), and \( T_{g,exp} \), all in Kelvin, are the long-term storage temperature, active glass transition temperature, and the stabilizing excipient glass transition temperature, respectively. Eqn. (1) can only be used when \( T_{g,exp} > T_{g,act} \) and \( T_{g,exp} > T_{st} + 50 \text{ K} \). For example, if trehalose is to be used as a glass-forming excipient with a dry \( T_{g,exp} \) of 390 K (~117 °C) (Drake et al., 2018) to stabilize an active with a \( T_{g,act} \) of 323.15 K (50 °C), more than 42 % w/w of the formulation should be composed of trehalose for the product to be stable at a storage temperature, \( T_{st} \), of 298.15 K (25 °C). For storage at a temperature of 313.15 K (40 °C), more than 65 % of the system should be composed of trehalose and for storage at a temperature of 343.15 K (70 °C), the product cannot be stabilized with trehalose at all.

In addition to their anti-plasticizing effect, some glass-forming excipients can be used to stabilize sensitive biologics such as bacteriophages, vaccines, and proteins in spray-dried platforms (Carriaga et al., 2019a; Gomez et al., 2021a). The reasons for this protective property are believed to be twofold: first, the hydrogen bonds formed between water and protein molecules are replaced with new bonds formed during drying between the hydroxyl groups of the stabilizers and the proteins, and second, the immobilization of the proteins in a glassy matrix significantly reduces the risk of different forms of denaturation (Hinrichs et al., 2001; Mensink et al., 2017). The required mass fraction of the glass former is believed to depend on the stabilizer and the biological entity, but a minimum mass ratio of 1:1 was shown to result in acceptable physical stability in several studies (Massant et al., 2020; Shepard et al., 2021).

2.2.2 Dispersibility enhancers and shell formers

As mentioned before, and as shown in Fig. 4, spray-dried particles (in particular, those made of small-molecule
compounds) are usually amorphous with smooth surfaces and high surface energies (Alhajj et al., 2021). When combined with the small size of the particles, especially those intended for pulmonary delivery, these properties result in cohesiveness that causes poor powder flowability and undesirable aerosol properties (Jüptner and Scherließ, 2019). To diminish these problems, another class of excipients, usually called shell formers or dispersibility enhancers, are included in the spray-dried formulations. The shell formers are intended to precipitate first on the surface of the dried particles and improve the aerosol properties of the powders via two mechanisms: first, they increase surface rugosity and hence decrease the contact area with the surrounding particles or external surfaces (Baldelli and Vehring, 2016); second, they decrease surface energies (Jong et al., 2016; Zhou et al., 2015). Both of these mechanisms reduce the cohesive (interparticle) and adhesive (extra particle) forces. Because it forms solid shells around the interior core of the particles, this kind of excipient might also protect the valuable actives or biologics from different surface-mediated degradation mechanisms (Carrigy et al., 2019b; Gomez et al., 2021b) or in some cases provide short-term protection against moisture-induced interparticle fusion (Li L. et al., 2016; Wang Z. et al., 2021b).

For maximized encapsulation, all shell formers need to precipitate or solidify before other components on the surface of the droplets during evaporation. Certain properties, such as low crystalline or amorphous solubility, large molecular size, and high surface activity can cause early shell formation. For instance, materials with low solubilities can solidify first during drying and tend to accumulate on the surface of the droplet until a solid shell is formed, while large molecules enrich the surface and reach their precipitation limit faster than smaller compounds. For example, some of the polysaccharides and other polymeric compounds, such as pullulan, Eudragit, and maltodextrin, produce a shell early during the evaporation process and can act as a shell former by increasing the surface rugosity (Bin Karim et al., 2021; Carrigy et al., 2019d; Zhang et al., 2018). Surface activity is another important attribute that can cause surface accumulation of excipients. The interfacial adsorption of surface-active molecules decreases the surface energy of the dried particles because of the outward orientation of their hydrophobic tails (Jong et al., 2016; Vartiainen et al., 2016). Furthermore, some surface-active shell formers, like trileucine (Carrigy et al., 2019b; Lechuga-Ballesteros et al., 2008; Ordoubadi et al., 2021a), undergo early phase-separation near the droplet surface resulting in highly rugose particles with decreased contact area (Wang H. et al., 2019). Some of the most effective shell formers have two or more of these properties. For example, both leucine and trileucine are surface-active and have low solubilities resulting in surface adsorption as well as early solidification during droplet evaporation (Lechuga-Ballesteros et al., 2008; Ordoubadi et al., 2021a; 2021b).

2.3 Process parameters
2.3.1 Feedstock preparation

Spray drying is essentially a method of desiccating liquid
feedstocks into a dry powder form composed of microparticles. A typical spray drying process involves feedstock preparation, atomization of the feedstock to form droplets, desiccation of the atomized droplets in a drying chamber, and separation of the dried particles from the drying gas (Cal and Sollohub, 2010). Carefully designed formulations intended for spray drying need to be presented in a liquid form before they can undergo subsequent atomization and drying processes. The feedstock preparation process for actives or excipients that are soluble in the selected solvent system is relatively straightforward and usually involves mixing the solid and liquid phases at appropriate conditions with additional agitation if needed. Despite the simplicity of preparation for solution-based feedstocks, spray drying from a homogeneous solution can have many variations and, if properly designed, can produce particles with multifunctional structures, such as layered, hollow, dimpled, porous, etc. (Vehring, 2008). A more in-depth discussion on this topic will be provided in the particle formation section.

Because a large proportion of all new drug candidates entering the development pipeline face various problems due to their poor aqueous solubility (Nagarwal et al., 2011), suspensions have become a popular dosage form of medication in drug delivery applications (Rabinow, 2004). For the same reason, the preparation of a stabilized suspension or emulsion feedstock is the most common modification to the simple solution-based spray drying process (Chaubal and Popescu, 2008; Dollo et al., 2003; Kumar et al., 2014; Soottitantawat et al., 2003). These two-phase systems are sometimes also employed to transfer some of their pre-existing structural properties onto the final dry particles. Two typical examples are the hybrid large porous nanoparticle aggregates reported by Tsapis et al. (Lintingre et al., 2016; Tsapis et al., 2002) and the porous PulmoSphere™ lipid particles summarized by Weers et al. (Weers and Tarara, 2014). Careful selection of surfactants assisted by a powered mixing process such as high shear mixing or high-pressure homogenization is usually needed to produce stable suspension feedstocks for the production of consistent products throughout the spray drying process (Chaubal and Popescu, 2008; Dollo et al., 2003; Singh and Van den Mooter, 2016; Verma et al., 2011).

More complex multi-phase systems with more than two dispersed phases such as feedstocks with multiple suspended solid materials, feedstocks with multiple emulsions, and emulsion-based feedstocks with additional suspended solids have been explored to meet more specific formulation design targets. For instance, feedstocks consisting of calcium salts dispersed in an aqueous Eudragit polymeric suspension were spray dried to produce microencapsulated particles for a controlled gastrointestinal release profile (Oneda and Ré, 2003). A complex dispersion of polymeric nanocapsules containing an oil core was spray dried with colloidal silica to form nanoparticle-coated microparticles (Tewa-Tagne et al., 2006; 2007). Orange oil was encapsulated in the inner compartment of another double emulsion by spray drying for better protection of the inner material (Edris and Bergnstahl, 2001). Micronized drug particles such as budesonide, ciprofloxacin, and amphotericin B were suspended within an oil (perflubron)-in-water emulsion feedstock and spray dried to produce drug-loaded composite particles for inhalation (Weers et al., 2019). Many of the studies referenced here employed multi-step feedstock preparation processes in which precursors were manufactured prior to the preparation of the final feedstock, an approach that is being increasingly used in complex formulations (Vehring, 2008).

2.3.2 Atomization, drying, and collection

Atomization of feedstocks into liquid sprays significantly increases the specific surface areas of the liquid phase that are exposed to the drying gas, thereby effectively facilitating rapid heat transfer from the heated drying gas to the atomized droplets and mass transfer of volatile solvents to the gas phase (Cal and Sollohub, 2010). Various atomizer designs based on different liquid disintegration mechanisms have been used to break up liquid feedstocks for the formation of dried particles with the desired physicochemical and morphological attributes. The most commonly used atomizer types can be generally categorized into rotary atomizers, hydraulic nozzles, pneumatic nozzles, and ultrasonic nozzles (Cal and Sollohub, 2010; Santos et al., 2018).

Among these, pneumatic nozzles, also known as multi-fluid nozzles, are the most popular atomizer for pharmaceutical applications (Cal and Sollohub, 2010). The most common configuration of such devices is based on a two-fluid nozzle atomizer in which the liquid feedstock is supplied to the nozzle, met by compressed atomizing gas, and atomized due to the high frictional forces between the two mixing fluids. Pneumatic atomizers are known for their ease of operation, good control over resulting particle size, applicability to different types of feedstocks, and wide range of throughput, all of which characteristics make them suitable for various applications from lab-scale research to industrial mass production (Santos et al., 2018). In terms of size coverage, which is a critical specification for atomizers, pneumatic nozzles can usually produce droplets in the 5–200 μm diameter range. The exact droplet size distribution for each atomizer can be affected by multiple parameters including the atomizer design, feedstock properties, and liquid and gas supply rate, etc. (Santos et al., 2018) and therefore needs to be calibrated for a better prediction of the final particle properties (Hoe et al., 2014).

As a rapid process of energy and mass exchange between the atomized droplets and the surrounding drying gas in a controlled environment, the drying process is where the liquid formulation eventually solidifies into solid particles. Many critical parameters are involved in this process.
Temperature and vapor activity inside the drying chamber are two of the main parameters that need to be carefully controlled and monitored: the temperature affects the particle formation process and the resultant particle morphology and structure, while vapor activities can have a major impact on the long-term physicochemical stability of the final powder product (Carrigy and Vehring, 2019). Thermodynamic modeling of the drying process has been used to predict the outlet temperature and relative humidity for different inlet conditions (Carrigy and Vehring, 2019; Ivey and Vehring, 2010); the concepts underlying this approach can be equally applied to different systems for an expedited formulation and spray drying process development (Carrigy et al., 2018; Wang H. et al., 2020).

A particle separation procedure needs to be implemented to collect dried particles seeded in the drying gas at the end of the drying process. The device most commonly employed for such purposes, the cyclone separator, uses centrifugal forces to collect particles from the gas flow supplied into a cylindrical chamber tangentially (Baumann et al., 2021). Fine particles smaller than the cut-off aerodynamic diameter of a specific cyclone operated at the corresponding gas flow rate will be expelled from the cyclone in an inner countercflow vortex to the exhaust, while larger particles will be collected (Santos et al., 2018). Bag filters based on fabric filtration technologies are another particle separation method used extensively in spray drying processes and feature high collection efficiency even for submicron particles, especially when a series of filters with gradually downsized pores are used (Cal and Sollohub, 2010). Other techniques such as scrubbers and electrostatic precipitators are also used for particle collection in various spray drying applications (Dobrowolski et al., 2018).

The initial studies and research on new formulations are frequently performed on small-scale or laboratory-scale spray dryers, which, compared to pilot-scale and production-scale dryers, generally have lower production rates and yields due to their smaller drying chambers and smaller production batches (Poozesh and Bilgili, 2019). The transition to larger dryers requires an informed methodology development that involves process scale-up, relating to the thermodynamic aspects, and formulation scale-up, relating to the particle formation mechanisms (Gil et al., 2010).

### 3. Particle formation theory

#### 3.1 Generation of solid particles during solvent evaporation

The primary size distribution of spray-dried particles is an important parameter that should be considered carefully during process and formulation design in accordance with the intended application of the powder. For example, for oral lung delivery it is customary to spray dry particles with aerodynamic diameters in the range of one to five micrometers (Dabbagh et al., 2018; El-Gendy et al., 2011), whereas larger particles are acceptable for nasal (Calmet et al., 2019; Kiaee et al., 2018) and other routes of delivery (Ferreira et al., 2020; LeClair et al., 2018). Assuming they are roughly spherical in shape, the mass median aerodynamic diameter (MMAD) of the spray-dried particles can be approximated by (Vehring, 2008)

\[
\text{MMAD} = \frac{6}{\pi} \left( \frac{\rho_p}{\rho} \right)^{1/3} C_v^{1/3} \frac{F_0}{F} \left( \frac{d_0}{d_{\text{MMAD}}} \right)^{7/2}
\]

Here MMD\(_0\), a process parameter, is the mass median diameter of the atomized droplets (equal to the initial droplet diameter, \(d_0\), for monodisperse sprays), which is a function of atomization parameters such as the atomizing pressure and the liquid feed flow rate for a twin-fluid atomizer (Hoe et al., 2014; Ivey et al., 2018); \(\rho_p\) and \(\rho'\) are the density of the solid particles and the reference density of 1 mg/mL, respectively; and \(C_v\) is the total feed concentration, a formulation parameter. It is evident from Eqn. (2) that the size distribution of the dried particles is strongly influenced by the atomized droplet distribution, with weaker sensitivity to the other variables, such as the commonly unknown particle density for which only a rough estimate is required due to the sixth root dependence. This relatively simple but practical equation does not describe the internal distribution of different components and does not consider their instants of solidification, for which the diffusion equations inside the evaporating droplets need to be solved (Gac, 2022).

Upon atomization into the drying chamber, the droplets may cool down or heat up depending on the initial feed temperature and the wet-bulb temperature of the solvent system (Chen X.D., 2008), with possible collision and coalescence of the droplets (Boel et al., 2020). After the brief initial transient stage, the temperature and evaporation rate of each droplet are stabilized and the constant-rate drying starts based on the \(d^2\)-law (Baumann et al., 2021; Vehring et al., 2007). The recession of the droplet surface due to rapid evaporation causes the concentration of solutes to rise near the surface. This induced concentration gradient causes a radially inward movement of the solutes in accordance with Fick’s law of diffusion. The constant-rate evaporation continues until the start of solidification, when the solvent can no longer evaporate unhindered. At this point, the temperature inside the droplet rises rapidly based on the local temperature and vapor activity inside the drying chamber, and solidification is completed with further loss of the solvent. The actual shape and morphology of the final dried product are related mostly to the rheological and physical properties of the solids, the process conditions, and the solvent system, which, in some cases, can cause inflation, deflation, or rupture of the particles (Baumann et al., 2021; Ordoubadi et al., 2021b; Vehring, 2008; Walton, 2000).

The mass transfer equations governing the diffusion
Diffusion inside evaporating droplets

As previously explained, the rapid evaporation of the solvents causes surface accumulation of solutes which in turn results in solute diffusion from the surface towards the center (Boraey and Vehring, 2014; Nandiyanto and Okuyama, 2011). Because of the small size of the droplets, it can be assumed that during the constant-rate evaporation stage the droplets are already moving with minimal relative velocity with respect to the drying medium, and the effects of shear stresses on the internal convective circulation can be neglected. Therefore, the mass transfer equations can be solved in a spherically symmetric manner in the radial direction only (Ordoubadi et al., 2019). Based on this assumption, the governing mass transfer equation for solute \( i \) inside an evaporating droplet is as follows:

\[
\frac{\partial C_i}{\partial t} = \frac{4D_i}{R^2} \left( \frac{\partial^2 C_i}{\partial R^2} + \frac{2}{R} \frac{\partial C_i}{\partial R} \right) - \frac{\kappa R}{2d^2} \frac{\partial C_i}{\partial R}
\]

where \( C_i \) is the temporal concentration of the solute at the dimensionless radial coordinate \( R = 2rd \), \( r \) is the radial coordinate here, and \( d \) is the time-dependent droplet diameter, while \( D_i \) and \( \kappa \) are the diffusion coefficient of the solute and the evaporation rate of the droplet, respectively. The evaporation rate is a measure of the rate of the decrease of the droplet surface area or

\[
\kappa = -\frac{dd^2}{dt}
\]

The parabolic partial differential equation for the mass diffusion (Eqn. (3)) can be solved numerically through integration in time using the initial condition \( C_i = C_{0i} \) and boundary conditions \( \partial C_i / \partial R = 0 \) at \( R = 0 \) and \( D_i \partial C_i / \partial R - (\kappa / 8)C_i = 0 \) at \( R = 1 \) (Ordoubadi et al., 2019). Here, \( C_{0i} \) is the initial concentration of the solute \( i \) in the feed solution. The solution of Eqn. (3) for each solute gives the concentration of that component for each instance and at each radial location that can be used to predict their moments of solidification.

The behavior of different components under different drying conditions was previously quantified by the Péclet number as defined below (Vehring et al., 2007):

\[
P_{ei} = \frac{\kappa}{8D_i}
\]

This dimensionless number illustrates the relative significance of the recession of the droplet surface due to evaporation and the diffusion of the solutes. A very large Péclet number \((P_{ei} \gg 1)\) means that the evaporation rate is so rapid that the solute molecules do not have enough time to diffuse towards the center and the result will be a very sharp concentration gradient near the surface, with the interior concentration values being close to the initial mean concentration for most of the evaporation period. A small Péclet number \((P_{ei} \ll 1)\) denotes the fact that the evaporation is slow and the solute molecules can freely diffuse away from the interface, resulting in a rather constant radial distribution, approximately equal to the bulk concentration, that increases with time due to the decrease of the droplet volume. For a moderate Péclet number \((0.1 \leq P_{ei} \leq 20)\) there will be a smooth transition from a maximum concentration on the surface to a minimum at the center of the droplet. These three different conditions are shown schematically in Fig. 5. This discussion of the internal diffusion based on Eqn. (3) is true for non-surface-active components in molecular form. In the case of surface-active materials, Eqn. (3) needs to be modified to account for surface adsorption (Ordoubadi et al., 2021a; 2021c).

Spray drying at high Péclet numbers usually results in hollow particles such as those of polysaccharides, proteins, and other macromolecules (Bin Karim et al., 2021; Carrigy et al., 2019c; Hu et al., 2017; Shepard et al., 2021), while spray drying at low Péclet numbers usually results in solid spherical particles, such as spray-dried trehalose (Mah et al., 2019; Ordoubadi et al., 2019) and lactose particles (Wu L. et al., 2014). Besides the Péclet number, the moment and mechanism of phase separation and solidification also play an important role in the final morphology of the dried

![Fig 5](image-url) The effect of the Péclet number on the internal solute distribution during droplet evaporation at a specific time.
particulate as will be discussed later.

During the formulation design of multicomponent systems, especially amorphous solid dispersions and glass stabilized systems, special attention should be paid to the Péclet numbers of individual solutes, since a very large difference in their interior distribution might result in separate solidification of each component as opposed to co-amorphization into a uniform glassy matrix (Carriag et al., 2019c; Li N. et al., 2020; Ousset et al., 2018).

As mentioned before, regardless of the Péclet number, each solute will have a maximum concentration near the droplet surface. Hence, it has been customary to provide solutions to the diffusion equations in the form of the surface enrichment, $E_{s,i}$, divided by the mean concentration of that solute inside the droplet, $C_{m,i}$. Generally, the surface and mean concentrations change with time, while the surface enrichment asymptotically converges to a constant steady-state value, $E_{ss,i}$, during the constant-rate drying period. This asymptotic value can be approximated for different Péclet number regimes as (Boraey and Vehring, 2014)

$$E_{ss,i} = \frac{C_{s,i}}{C_{m,i}}$$

$$\approx \begin{cases} 
1 + Pe_i \frac{5 + Pe_i^2}{100 - Pe_i^3} & \text{if } Pe_i < 20 \\
Pe_i / 3 + 0.363 & \text{if } Pe_i \geq 20
\end{cases}$$

(6)

It has previously been shown that for Péclet numbers larger than 0.5 the time to reach steady-state surface enrichment might be a significant portion of the total droplet drying time, $t_d$ (Boraey and Vehring, 2014). Therefore, for these conditions ($Pe_i > 0.5$) the transient evolution of the surface enrichment needs to be approximated to accurately predict the diffusion-controlled particle formation during spray drying. Through correlation to numerical data, certain relationships have been suggested as a way to estimate the transient surface enrichment of solutes, $E_{s,i}(t)$, during droplet evaporation as shown below (Boraey and Vehring, 2014):

$$E_{s,i}(t) = \frac{C_{s,i}(t)}{C_{m,i}(t)}$$

$$\approx \begin{cases} 
\frac{E_{ss,i} - \exp(-n_1)}{1 - \exp(-n_1)} & \text{if } Pe_i < 0.5 \\
\frac{E_{ss,i} - 1}{1 - \exp(-n_1)} & \text{if } 0.5 < Pe_i < 25 \\
\frac{E_{ss,i} - \exp(-n_2)}{1 - \exp(-n_2)} & \text{if } 25 < Pe_i < 200 \\
\frac{E_{ss,i} - \exp(-n_3)}{1 - \exp(-n_3)} & \text{if } Pe_i \geq 200
\end{cases}$$

(7)

Here $n_1 = 15Pe_i^{-0.7}$, $n_2 = 0.95$, $E_{ss,i} = 0.858E_{ss,i}$, and $t_d = d_i^2 / \kappa$ is the droplet drying time based on the constant-evaporation assumption, while $d_i$ is the initial droplet diameter and $\kappa$ is the evaporation rate defined in Eqn. (4) and provided for some of the solvents in Fig. 7. The relationships in Eqn. (7) can be used for Péclet numbers ranging from zero to two hundred, which span a broad array of conditions for spray drying applications ranging from small molecules to large suspended nanodroplets. For example, the Péclet numbers of trehalose dissolved in water (an example of a small-molecule excipient or active) and an aqueous nanoemulsion with an average droplet size of 100 nm (an example of a very large aggregate or

![Fig. 6](https://example.com/fig6.png) The time evolution of surface enrichment, $E_{s,i}(t)$, normalized by the steady-state surface enrichment, $E_{ss,i}$ (Eqn. (6)), versus the normalized time for different Péclet numbers, obtained from the correlations given in Eqn. (7). Here, $t_d = d_i^2 / \kappa$ is the droplet drying time.

![Fig. 7](https://example.com/fig7.png) The evaporation rates and droplet temperatures of several solvents frequently used in pharmaceutical spray drying at different drying temperatures. The values were calculated using a full numerical model.
biophysics, both drying at a temperature of 100 °C (in a
typical range of drying temperatures for the spray drying
of pharmaceutical particles) are 1.25 and 153, respectively.
These numbers were calculated using Eqn. (5); the numeri-
cal values for the evaporation rate and diffusion coefficients
will be discussed in the next two subsections.

The evolution of surface enrichment with time for a range of Pécelt numbers is shown in Fig. 6. It is apparent
from these profiles that for larger Pécelt numbers corre-
sponding to the spray drying of larger solutes or at higher
temperatures, the transient behavior of surface enrichment
is more significant than for smaller Pécelt numbers.
For such conditions, the use of the correlations given in
Eqn. (7) is the most accessible and practical method for
approximating the surface concentration of each solute.

After the calculation of surface enrichment with the help
of Eqn. (7), the actual surface concentration of each solute at
each time, \( C_{m,i}(t) \), can be obtained from

\[
C_{m,i}(t) = E_{m,i}(t) \frac{C_{0,i}}{C_{m,i}(t)}
\]

in which \( C_{m,i}(t) \) is the mean concentration of solute \( i \) inside
the droplet, which can be obtained from a mass balance
equation compared to the initial state of the atomized
droplet as follows:

\[
C_{m,i}(t) = C_{0,i} \left(1 - \frac{t}{t_d} \right)^{-3/2}
\]

Here, \( C_{0,i} \) is the initial feed concentration of solute \( i \) and,
as mentioned before, \( t_d = \frac{d^2}{\kappa} \) is the drying time of the
droplet assuming a constant evaporation rate.

During the actual formulation design, the surface con-
centration of all excipients and actives can be calculated
for \( 0 \leq t \leq t_d \) and compared to their respective solidification
thresholds to determine which component is expected to
precipitate first, as will be discussed in later sections.

### 3.3 Evaporation rates

As seen in Eqn. (3), the evaporation rate of the droplets is
one of the determining factors of particle formation and
solidification. For single-solvent systems, the evaporation
rate can be assumed to be constant throughout the drying
stage, neglecting the initial stabilization of the droplet
temperature and the final decrease due to solute enrichment
(Boel et al., 2020). On the other hand, solvent composition
and evaporation rate vary with time for multi-solvent
systems due to the different volatility of the solvents and
any non-ideal effects (Ordoubadi et al., 2019). For this
reason, the evaporation rates of multi-solvent systems
should be predicted using full numerical methods and al-
gorithms as explained elsewhere (Ordoubadi et al., 2019).
In this subsection, the evaporation rates and the droplet
temperatures of some of the solvents most frequently used
in the spray drying of pharmaceuticals and biologics are
presented. To this end, a numerical model, verified and
validated previously (Gregson et al., 2019; Ordoubadi et
al., 2019), was used to calculate the evaporation behaviors
of microdroplets composed of water, acetone, ethanol,
methanol, dichloromethane (DCM), and tetrahydrofuran
(THF). The evaporation rates, defined as \(-\frac{d\rho}{dt}\), and the
droplet temperatures of these solvents drying at different
drying temperatures and zero vapor activity (dry condition)
are shown in Fig. 7. The equilibrium droplet temperature,
which is close to the wet-bulb temperature, is important in
determining the temperature-dependent properties of the
solutes, such as the diffusivity coefficient and the solubility.
This temperature is also of significance in choosing the op-
timal process conditions so as not to subject temperature-
sensitive biologics to conditions outside of their tolerance.
The drying temperature can be conservatively approxi-
mated as the inlet temperature of the spray dryer, even
though the actual temperatures and vapor activities in the
vicinity of a spray plume inside a spray dryer vary sig-
ificantly and are generally unknown for all the possible
processing conditions (Longest et al., 2020). It can be seen
from Fig. 7 that the equilibrium temperatures of these
solvents drying at temperatures as hot as 200 °C barely
reach 40 °C, pointing to the inherent advantage of the
spray drying process in protecting sensitive molecules and
biological entities from elevated temperatures due to the
evaporative cooling effect.

### 3.4 The diffusion coefficients

In the absence of any experimental data for the diffusion
coefficients of the solutes in the solvent of interest, which
is usually the case for newly discovered drugs or biologics,
the Stokes-Einstein equation can be used as an approxima-
tion, as shown below (Bird et al., 2006; Zmpitas and Gross,
2021),

\[
D_{i,j} = \frac{k_B T_0}{3\pi\mu d_i}
\]

where \( D_{i,j} \) is the diffusion coefficient of solute \( i \) in sol-
vent \( j \) at infinite dilution, \( k_B=1.38 \times 10^{-23} \text{m}^2\text{kg}\cdot\text{s}^{-2}\text{K}^{-1} \)
is the Boltzmann constant, \( T_0 \) is the droplet temperature
in Kelvin, which can be obtained from Fig. 7, \( \mu \) is the
dynamic viscosity of the solvent at the droplet temperature
in Pa·s, presented in Fig. 8, and \( d_i \) is the hydrodynamic
spherical diameter of the molecule or particle of interest in
m obtained from \( \sqrt{6V_j/\pi} \). Here, \( V_j \) is the molecular volume
in m³ that can be obtained via different methods (Bird et al.,
2006; Edward, 1970; Kooijman, 2002; Zmpitas and Gross,
2021), for example, by using the Van der Waals volumes
obtained from the atomic and group incremental volumes
(Blokhina et al., 2017; Bondi, 1964; Edward, 1970). The
hydrodynamic diameters of some of the excipients and
APIs used in the formulation of pharmaceutical solid
particles were calculated based on their Van der Waals
volumes (Edward, 1970) and are presented in Table 1. The
molecular volumes of these compounds were determined based on their neutral and anhydrous forms.

The Stokes-Einstein equation should be used with the knowledge that it gives accurate results only for dilute solutions and for solute molecules that are relatively spherical and much larger than the solvent molecules. The concentration-dependency of the diffusion coefficient becomes significant only near the end of droplet evaporation and hence can be neglected for practical uses of particle formation theory. It should be noted that the use of the molecular diameters in Eqn. (10) is not reasonable when the solutes are not in molecular solution form. For example, when the solutes or actives are present in the form of liposomes, micelles, emulsions, nanoparticles, or nanocrystals, the approximate size of these larger aggregates should be used to estimate their diffusion and surface enrichment inside the evaporating droplets.

The use of atomic and group contribution methods in determining the size of macromolecules, such as proteins and polymers, is not straightforward. For such compounds, the use of available correlations and relationships of molecular volume versus molar mass is recommended. For example, the following correlation was obtained via nanoelectrospray gas-phase electrophoretic mobility molecular analysis for proteins (Weiss et al., 2018):

$$d_{\text{prt}} = 1.61(M_{\text{prt}})^{0.343}$$ (11)

Here, $d_{\text{prt}}$ is the molecular diameter of a protein in nm and $M_{\text{prt}}$ is the molar mass in kDa.

3.5 The onset of solidification or crystallization

The solution of the mass transfer equations inside an evaporating droplet results in the concentration of each component at different times at each radial coordinate, but as soon as one of the components starts to solidify, either due to crystallization or amorphous phase separation, the concentrations are suspected to change rapidly. This is because the evaporation rate is expected to decrease upon shell formation (Boel et al., 2020) and the local sites of solidification can act as source points that result in concentration profiles with sharp gradients (Douglass and Harrowell, 2018; Fukui and Maeda, 1998) unlike those predicted by Eqn. (3). Based on these complications, one straightforward method of predicting the surface composition of the spray-dried particles is to determine which component solidifies first and assume that this solute will have the highest amount of surface coverage on the final particles. To this end, the time evolution of surface concentrations of all solutes can be compared to a critical concentration for each material. Once this concentration is reached the solidification is expected to commence for that solute. The compound that reaches its critical concentration earlier than the other solutes is then expected to be the dominant component on the surface of the particles. The exact prediction of the actual surface compositions is complicated and requires knowledge of the phase diagram of the system including all of the solutes and solvents, which is difficult to obtain for newly discovered drugs and biologics.

The estimation of the solidification thresholds depends on the ability of the material to form a crystal or glass during drying; hence, APIs and excipients can be characterized by their tendency to crystallize during spray drying. The crystallization tendency is related to many factors, including glass transition and melting temperatures.

![Fig. 8](image-url) The dynamic viscosity values of several solvents frequently used in pharmaceutical spray drying at different droplet temperatures (Yaws, 2010).

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Hydrodynamic Diameter (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose/Trehalose/Sucrose</td>
<td>0.82</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.68</td>
</tr>
<tr>
<td>Raffinose</td>
<td>0.93</td>
</tr>
<tr>
<td>Leucine</td>
<td>0.64</td>
</tr>
<tr>
<td>Trileucine</td>
<td>0.89</td>
</tr>
<tr>
<td>Glycine</td>
<td>0.51</td>
</tr>
<tr>
<td>DSPC</td>
<td>1.17</td>
</tr>
<tr>
<td>DPPC</td>
<td>1.14</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>0.93</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>0.90</td>
</tr>
<tr>
<td>Beclometasone</td>
<td>0.97</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>0.77</td>
</tr>
<tr>
<td>Formoterol</td>
<td>0.85</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.92</td>
</tr>
<tr>
<td>Vilanterol</td>
<td>0.94</td>
</tr>
<tr>
<td>Etravirine</td>
<td>0.86</td>
</tr>
</tbody>
</table>
solubility, the solvent system used, processing conditions, molecular size, and crystal structure (Kawakami, 2019); hence, the prediction of the final solid phase of spray-dried material is complicated. In the absence of any literature data, the ability of a material to crystallize during spray drying can be measured via powder X-ray diffraction or Raman spectroscopy on an initial spray-dried batch of the excipient or active of interest during the early stages of formulation development.

The critical concentrations that can be used as a threshold to compare with the instantaneous solute concentrations depend on the predicted mechanism of solidification or dissolution as will be explained below.

3.5.1 Crystallizing compounds

For crystallizing compounds, crystalline solubility has frequently been regarded as the concentration after which nucleation and crystal growth commence (Vehring, 2008). However, based on the classical nucleation theory, a certain level of supersaturation is required for any system to undergo crystal growth due to the nucleation barrier (Karthika et al., 2016). When the concentrations are increased above this minimum supersaturated value, the time of nucleation decreases until crystallization can be assumed to be instantaneous (He G. et al., 2006). Considering the very high rate of the evaporation of droplets during spray drying, this critical supersaturated concentration, rather than the solubility, can be deemed a threshold of nucleation and crystal growth in the formulation design of spray-dried particles (Ordoubadi et al., 2021b; Z. Wang Z. et al., 2021a).

By measuring the nucleation times of a variety of materials dissolved in several evaporating microdroplets at different conditions, He et al. proposed a semi-analytical method of calculating the critical supersaturation ratio at which nucleation would be instantaneous (He G. et al., 2006). Such methods still require the measurement or approximation of certain properties that are not readily available, such as the water activity coefficient at saturation. Hence, the actual crystalline solubility can still be used as a first approximation in the particle formation models in the absence of these data.

3.5.2 Glass formers

Most of the newly discovered drugs and biologics do not crystallize during spray drying but instead phase separate into glasses or amorphous materials (Baumann et al., 2021; Wang B. et al., 2021). The precipitation of a material into an amorphous state rather than a crystalline form takes place when the metastable region (between the crystalline solubility and spinodal curves) is traversed fast enough not to permit nucleation and growth (Zallen, 1998). Shown schematically in Fig. 9, this phenomenon starts immediately after atomization from the initial solute concentration, $C_{oI}$, at the droplet temperature, $T_d$, and moves isothermally into the supersaturated and unstable regions due to evaporation. Note that the initial temperature stabilization of the droplet is ignored in this figure. Upon reaching the spinodal point, precipitation commences based on glass-liquid phase separation (solute-rich glass and solvent-rich liquid) or liquid-liquid phase separation (solute-rich gel and solvent-rich liquid) depending on the plasticization behavior of the system (Douglas and Harrowell, 2019). At this point, the droplet temperature increases due to the decrease in evaporation rate, and eventually the solid particle forms, making a mixture with the remaining residual solvent (Charlesworth and Marshall, 1960).

The presence of multiple glass-forming compounds in the formulation introduces complexities that require multi-phase analysis to model the co-amorphization of all components in a manner similar to the studies conducted for the preparation of amorphous solid dispersions (Davis et al., 2017; Ziaee et al., 2017). For simplicity, during the early stages of formulation design of such systems, it can be assumed that each solute precipitates in the solvent system independently, with the effects of the other components being neglected.

Particle engineers and formulators can use the concept of amorphous solubility for each glass former in the system to determine which component precipitates first. Compared to crystalline solubility, the amorphous solubility, especially of small molecules, is more difficult to determine experimentally because of the precipitation of the excess dissolved material as crystals (Douglas and Harrowell, 2018). Based on thermodynamic considerations, the amorphous solubility of a material, $C_{aI}$, at temperature $T$ can be obtained from its crystalline solubility, $C_{cI}$, using Eqn. (12) (Almeida E Sousa et al., 2015; Ilevbare and Taylor, 2013),

$$C_{aI} = C_{cI} \cdot \exp[-I(\Delta f)] \cdot \exp\left(\frac{\Delta G_{am}}{RT}\right)$$

where $\Delta G_{am}$ is the difference in free energy of crystalline
and amorphous states, \( I(a_s) \) is related to the activity of the amorphous state saturated with the solvent, and \( R \) is the universal gas constant. The free energy difference can be obtained from (Almeida E Sousa et al., 2015; Hoffman, 1958),

\[
\Delta G_{ac} = \frac{\Delta_f H \cdot (T_m - T) \cdot T}{T_m^2}
\]  

(13)

in which \( \Delta_f H \) is the enthalpy of melting and \( T_m \) is the melting temperature of the crystal, both of which are obtainable from differential scanning calorimetry (DSC). The activity term, \( I(a_s) \), can be obtained from the integration of the water sorption isotherm of the amorphous solid, which can itself be obtained from dynamic vapor sorption (DVS) measurements as explained in (Murdande et al., 2010).

Alternatively, the instant of phase separation of glass formers in evaporating microdroplets can be directly measured via single-particle measurements, as was previously done for trehalose (Ordoubadi et al., 2021b).

### 3.5.3 Surface-active compounds

Some excipients and biopharmaceutical actives are amphiphilic, meaning that they possess a hydrophobic tail as well as a hydrophilic head group, making them a surface-active agent, or simply a surfactant, with a tendency to be adsorbed on air-water interfaces (Rosen and Kunjappu, 2012). This adsorption on the interface is observed macroscopically via the decrease in surface tension of the solution. During spray drying and droplet shrinkage, the internal diffusion of surface-active materials is different from that shown in Eqn. (3) for non-surface-active solutes. The exact mechanisms of particle formation and diffusion of surface-active molecules have been discussed previously (Ordoubadi et al., 2021a). In short, immediately after atomization, the surface of the droplets acts as a sink for such molecules. These molecules are then adsorbed into a monolayer on the interface causing a drop in local free concentration underneath the surface. This decrease in solution concentration causes an outward radial flux of the surface-active molecules towards the interface. The surface adsorption continues until the monolayer becomes saturated with these molecules, after which further evaporation might cause the adsorbed molecules to dissolve back into the solution to maintain stability.

For surface-active excipients or APIs, the time to form a saturated monolayer on the surface can be counted a design criterion and compared to the precipitation thresholds of other components. This is because a surface-active dispersibility enhancer needs to make a saturated monolayer on the surface before the precipitation of other components so that the final dried particle will contain a fully packed hydrophobic shell. This shell can potentially decrease the surface energy of the particles and possibly result in wrinkled surfaces, which would in turn improve aerosol properties (Mangal et al., 2015; 2019; Wang H. et al., 2019). It should be noted that besides making the monolayer, the surface-active molecules will eventually either crystallize or phase separate into a glass based on the previous discussions. For example, trelecucine is expected to make a monolayer first and then solidify into an amorphous material at a later stage during droplet evaporation (Ordoubadi et al., 2021a).

The surface adsorption of surface-active compounds is kinetically controlled by two sequential phenomena: 1) diffusion of the molecules towards the surface, and 2) adsorption and reconfiguration of the molecules into the monomer (Eastoe and Dalton, 2000; Jayasundera et al., 2009). Hence, the calculation of the instant of monolayer formation on the surface of a droplet is related to the diffusion coefficient of the surface-active compound, its maximum surface excess concentration, \( \Gamma_{\text{max}} \), and its size and complexity. The maximum surface excess concentration, with the dimension of kg/m² or mol/m², is the maximum amount of surfactant molecules that can become adsorbed on an interface and is a measure of surface activity (Rosen and Kunjappu, 2012). This property can be obtained from static surface tension measurements at different solute concentrations. Such a measurement, usually done using Wilhelmy plate, du Nouy ring, or pendent drop techniques results in a correlation between the static surface tension, \( \sigma \), and the solute bulk concentration, \( C_s \) (Ebnesajjad, 2011). By fitting an appropriate empirical isotherm to this data, the maximum surface excess concentration of each solute can be determined. For example, \( \Gamma_{\text{max}} \) in conjunction with the Langmuir adsorption constant, \( K_L \), are the two fit parameters in the Szyzkowski surface equation of state as seen below (Eastoe and Dalton, 2000):

\[
\sigma = \sigma_0 - nRT \Gamma_{\text{max}} \ln(1 + K_L C_s)
\]  

(14)

Here, \( n \) is equal to 1 for non-ionic or zwitterionic solutes and is equal to 2 for one-by-one ionic solutes, while \( R \) is the Universal gas constant, \( T \) is the solution temperature in Kelvin, \( \sigma \) is the surface tension in N/m, and \( \sigma_0 \) is the static surface tension of the solvent in the absence of any solutes. The maximum surface tension obtained directly from fitting Eqn. (14) to surface tension measurements has a unit of mol/m² that can be simply converted to other units such as mg/m² using the molar mass of the solute molecules. A typical surface tension measurement with a Szyzkowski fit to determine the maximum surface excess concentration is shown in Fig. 10. The critical micelle concentration (CMC) shown in this figure is a property of surfactant solutions and is the concentration above which no further decrease in surface tension is possible due to the formation of micelles.

As an example, and based on available tensiometry data at 25 °C (Gliński et al., 2000; Lechuga-Ballesteros et al., 2008), the maximum surface excess concentrations of
trileucine and leucine were approximated to be 0.99 and 0.15 mg/m², respectively. These numbers partially explain the better shell-forming capabilities of trileucine compared to leucine (Ordoubadi et al., 2021a; 2021b).

Assuming that the incorporation of the surface-active molecules into the monolayer occurs instantaneously (diffusion-controlled process), the time required to saturate a semi-infinite surface, \( t_{f,i} \), was calculated to be (He Y. et al., 2015; Ward and Tordai, 1946)

\[
t_{f,i} = \frac{n_i \Gamma_{2\text{max},i}}{4D_n C_{b,i}}
\]  

(15)

where \( \Gamma_{2\text{max},i} \), \( D_n \), and \( C_{b,i} \) are the maximum surface excess concentration of the surface-active solute \( i \), its diffusion coefficient, and its bulk concentration, respectively. This rough estimate for the time to monolayer formation was used previously to explain the particle formation of spray-dried formulations containing surface-active components (Adler and Lee, 1999; Kawakami et al., 2010; Landström et al., 2000) and can be used in the formulation design of such systems. The limitations of using this equation are that it does not account for the resistance to surface adsorption due to the already adsorbed molecules, nor does it take into consideration the delay in surface adsorption due to the reorientation of the molecules. Furthermore, as explained previously (Ordoubadi et al., 2021a), this simplified method cannot model the increase in solute bulk concentration during droplet evaporation or the possible depletion of the molecules for very small droplets. Regardless of these shortcomings, the use of Eqn. (15) is simple and practical for most formulation design applications.

### 3.5.4 Nanostructures

Research into the inclusion of nanostructures in spray-dried solid powders has grown in the last couple of decades (Johnson et al., 2020; Malamatari et al., 2020). This kind of formulation is possible through the preparation of a feed nanoemulsion or nanosuspension by dispersing liposomes (Maniyar and Kokare, 2019), nanodroplets (Gomez et al., 2019), nanoparticles (Tsapis et al., 2002; 2005), and other forms of immiscible nanostructures (Malamatari et al., 2020; Saallah and Lenggoro, 2018; Wang Z. et al., 2022). For such structures, the instant of close packing on the surface becomes the critical point during the drying stage since this is the point at which a shell can begin to form as these nanostructures come into close contact with each other. What happens after this point depends mostly on the interfacial forces between these nanostructures: the shell either collapses or maintains its rigidity and forms a hollow sphere (Ahumada-Lazo and Chen, 2022; Bahadur et al., 2011; Minoshima et al., 2001). The time of this close packing is important during the formulation design, regardless of what ensues afterward. As an example, a shell-forming excipient acts best if it makes a shell before the nanodroplets containing a biological entity do. To this end, the critical time of close packing for nanostructures can be calculated assuming a critical volume fraction of \( \sim 0.6 \) (Ahumada-Lazo and Chen, 2022; Minoshima et al., 2001). This value can be converted to mass fraction to result in a critical surface value for shell formation, \( Y_{nc} \), as

\[
Y_{nc} = \frac{3 \rho_{liq}}{2 \rho_n + 3 \rho_{liq}}
\]

(16)

where \( \rho_{liq} \) and \( \rho_n \) are the density values of the liquid feed and nanostructures, respectively. The critical concentration, \( C_{nc} \), in mg/mL, can then be obtained from

\[
C_{nc} = \frac{Y_{nc}}{\rho_n}\left(\frac{1 - Y_{nc}}{\rho_{liq}}\right)^{-1}
\]

(17)

Here the densities should have the same units as the concentration. The surface concentration of the nanostructures obtained from Eqn. (7) can then be compared to this critical value to obtain their time of shell formation, while their average diameter can be used in Eqn. (10) to find their diffusion coefficient.

### 4. The characterization techniques

As mentioned previously, the sample spray-dried powders need to be characterized to be assessed against certain predefined criteria. Depending on the specific formulation, these assessments might include both physical and chemical characterizations such as size distribution, morphology, solid phase, bulk density, and composition (Barona et al., 2021; Frank et al., 2022; Mangal et al., 2019; Nicholas et al., 2020). Some of the physical characterization techniques will be reviewed here.

#### 4.1 Morphology characterization

Frequently, the morphology of the spray-dried powders is the first factor to be studied. By looking at the micrographs of the particles, for example, one can...
determine qualitatively if the product is dispersible or flowable based on the surface rugosity; one can also detect individual particles as opposed to an agglomerate of fused particles. The instruments of choice for such observations are scanning electron microscopes (SEMs), which provide a surface topology by scanning the sample with an electron beam. The interaction of the electron beam with the sample results in the scattering and emission of electrons that are then collected on different detectors to result in a micrograph (Leonard et al., 2012). Ion microscopy can also be used in cases where much higher resolutions are required, coating of the samples needs to be avoided, or single particles are to be cut using focused ion beam milling to study the internal morphology (Heng et al., 2007; Ordoubadi et al., 2019). Sample micrographs of some batches of dried particles obtained from these methods are shown in Fig. 11.

The rugosity of the spray-dried powders can also be quantified through the measurement of the specific surface area via Brunauer–Emmett–Teller (BET) analysis relative to the geometric specific surface area, as was shown previously (Wang Z. et al., 2022).

### 4.2 Surface composition characterization

The surface composition of spray-dried engineered particles is critical to the validity of the formulation design. As an example, a shell former needs to contribute to most of the composition on the surface of spray-dried particles to have maximum benefits, while the valuable payload, whether biologics or APIs, should typically have minimal presence on the surface.

For surface characterization, two kinds of instruments are frequently used for spray-dried microparticles: time-of-flight secondary ion mass spectrometry (ToF-SIMS) and X-ray photoelectron spectroscopy (XPS). Fundamentally, ToF-SIMS detects ion fragments, while XPS is an elemental analysis. Both methods require relatively complicated post-processing procedures for quantification (Mangal et al., 2019; Nicholas et al., 2020; Wu X. et al., 2010); however, compared to XPS analysis, ToF-SIMS has a better lateral resolution and lower analysis depths (~1–3 nm for ToF-SIMS compared to ~5–10 nm for XPS) (Alhajj et al., 2021; Nicholas et al., 2020).

Energy-dispersive X-ray spectroscopy (EDX) has also been used to map the surface elemental compositions of microparticles (Eedara et al., 2016). This elemental method has a typical penetration depth of up to 1 μm, which makes the surface characterization of microparticles more difficult (Alhajj et al., 2021).

### 4.3 Solid-state characterization

Besides morphology, the solid phase of spray-dried powders is one of their most important characteristics.
conditions and is frequently measured by dynamic vapor sorption (DVS), which can also be used to indirectly measure the amorphous content of the sample (Sheokand et al., 2014).

The water content of spray-dried powders influences their stability and flowability and needs to be measured during the product characterization, as high water content can decrease the glass transition temperature through plasticization of the amorphous content of the powder (Shepard et al., 2020; Shetty et al., 2018). Karl Fischer titration is usually employed to measure the water content present in the powders either when it remains as residual solvent or is absorbed during storage and handling (Carrigy and Vehring, 2019).

5. Summary and conclusions

Spray drying can address many of the current and future challenges in the preparation of solid dosage forms and is the ideal manufacturing process for thermostable global health products. The mechanistic formulation design of spray-dried engineered microparticles is complex, with most of the available particle formation models requiring prior knowledge of the fundamental sciences behind them. Necessary information was provided to make the use of these models more straightforward and also to assist in the selection of appropriate excipients. Using such predictive tools during the early stages of product development can significantly reduce the number of experimental iterations and thus save time and effort. Several challenges remain that require in-depth studies and cannot be predicted via simplified theoretical analysis, such as the exact coprecipitation kinetics of glass mixtures or crystalline components, the final morphology of the particles, or the long-term stability of the product at different storage conditions. These emphasize the need for complementary experimentation.

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Authors’ Short Biographies

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Dr. Ordoubadi is a postdoctoral fellow in the Department of Mechanical Engineering at the University of Alberta. He holds a PhD from the University of Alberta focused on developing predictive tools to assist in the formulation design of spray-dried inhalable microparticles to reduce costs and risks during the early stages of product development of emerging therapeutics in solid dosage form. He is also experienced in using numerical simulations and computational fluid dynamics related to heat and mass transfer, multiphase flows, and aerosol mechanics.

Hui Wang

Dr. Wang obtained his BSc in Materials Science and Engineering from Southeast University in Nanjing, China. During his MSc and PhD studies with the Particle Engineering Group at the University of Alberta, he focused on designing and applying advanced characterization techniques, including cascade impaction, Raman spectroscopy, and shadowgraphic imaging, for the testing and optimization of inhalation formulations for pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). He has rich experience in design, production, testing, and pulmonary delivery of medicinal microparticles. He is currently a research scientist in the group, working on various projects related to respiratory drug delivery. His research interests include inhalation formulation development, pharmaceutical particle engineering, and microparticle encapsulation of biologics.

Reinhard Vehring

Dr. Vehring is a Professor in the Mechanical Engineering Department at the University of Alberta and holds the George Ford Chair in Materials Engineering. He graduated with a diploma in Mechanical Engineering from the Gerhard Mercator University in Duisburg, Germany, and received a doctorate from the University of Bochum in the field of molecular spectroscopy on microparticles. Dr. Vehring has held positions in academia and industry advancing aerosol science and particle technology for more than 28 years. Before returning to academia, he worked on pulmonary delivery of peptides, proteins, and small molecules at Nektar Therapeutics and was part of the team developing Exubera, the first inhalable insulin. Subsequently, he developed solid dosage forms for virus vaccines, monoclonal antibodies, and oncology therapeutics at Medimmune, and supported FluMist, the first nasally administered live attenuated influenza vaccine. Dr. Vehring was the lead inventor for the co-suspension formulation technology which is used by AstraZeneca to develop metered-dose inhaler-based therapeutics for respiratory diseases. At the University of Alberta, Dr. Vehring directs the Particle Engineering facility focusing on advanced micro and nanoparticle design and analysis.