Mechanistic Understanding of Microparticle Formation in Respiratory Applications

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Summary

This contribution summarizes recent advances in the mechanistic understanding of particle formation processes that provides the basis for microparticle based products with respiratory applications. Key mechanisms are heat and mass transport on evaporating or condensing droplets, internal redistribution of components in droplets by diffusion, phase separation processes like nucleation and crystal growth, and particle plasticity, such as shell buckling or collapse of porosity. Since the parameter space governing these processes is much too large for empirical studies, systematic experimental and modelling studies need to be undertaken.

Because of the complexity of actual manufacturing processes, experimental studies of particle formation are best conducted on idealised model systems. Progress on a variety of such experimental models is presented, ranging from highly idealised systems, like single particle levitation and droplet chains, to more representative ones like monodisperse spray drying and well-instrumented process equipment in combination with process models.

Analytical and numerical models for particle formation in single solvent and co-solvent systems provide predictive parameters that can be used in the engineering of microparticles. Application examples are shown for glass stabilization in amorphous systems, surface modifications in partially crystalline systems, and encapsulation of nano-emulsions.

Key Message

Fundamental understanding of the physico-chemical processes underlying microparticle formation allows development of predictive tools for particle design, thereby greatly accelerating product development, reducing risk and enabling sophisticated products based on nano-structured microparticles.

Introduction

In recent years, inhalation products have been commercialized that rely on structured microparticles for their functionality; several more are in development. Such products cannot be developed with simple micronized material, but rather require a more sophisticated particle morphology that cannot be designed by trial and error. Consequently, the discipline of particle engineering has seen a marked expansion, both in industry and in academia. Particle design for pulmonary applications uses predictive process models to find and control the critical parameters of the manufacturing process, adds solid phase modelling to formulation design to achieve the desired storage stability and environmental robustness, and is based in a mechanistic understanding of the physical processes that govern particle formation.[1] Many of these processes are still poorly understood, and modelling attempts are hampered by the lack of material properties, especially in non-equilibrium and supersaturation regimes. Hence, much systematic experimental work needs to be undertaken to advance the field.

This contribution will briefly describe several important sub-processes that occur in particle formation during spray drying and explain why they are important to master. Next, experimental techniques will be described that can be used to learn more about these processes. Finally, selected applications of a predictive particle design framework will be presented.

Particle Formation Processes in Spray Drying

One of the first tasks that one encounters when trying to describe a droplet drying process is to model the size change of the droplet as a function of time. For a single component, this is a simple task, requiring only the application of established textbook theory. More complex is the situation for co-solvent systems and in propellant droplet evaporation. In these cases the composition of the droplets can change over time, evaporation rates are no longer constant, and condensation of water onto the droplet can occur through evaporative cooling.[2] Knowledge of evaporation rates is essential for residence time calculations in spray dryers, since these rates determine the size of the equipment for a given production scale. The droplet size evolution of aerosols from pressurized metered dose inhalers, which can be treated as a special case of spray drying, is needed for lung deposition calculations, which can support dose finding. Furthermore, it is necessary to know the solvent composition in the droplets as a function of time, because otherwise it cannot be determined when individual actives or excipients begin to precipitate due to supersaturation. Adequate models need to take heat and mass transfer between droplet and gas phase into account and can only be solved numerically, except in the most simple cases.

The next step is to describe what happens inside the droplets during evaporation. In general, spray drying can be used for solutions, suspensions or even more complex feed stock like nanoemulsions. This fact means that the internal distribution of dissolved or suspended components with hugely varying mobility needs to be described. A

semi-analytical model can be developed for single solvent systems, if only the diffusion of components and the surface recession rate of the droplet are considered, e.g. in the form of a dimensionless number.[3] The results from such a model inform the particle designer about the sequence of precipitation events in the shrinking droplets and indicate which components tend to accumulate on the surface. They also provide information about the time available for precipitation events. Diffusion models are very helpful in designing the radial distribution of the dried particles, e.g. for encapsulation or dispersibility enhancement. In the future, more comprehensive models will be required that also incorporate the effects of surface activity of excipients like leucine or trileucine.[4]

Once dissolved components reach critical supersaturation, nucleation of a solid phase commences and the formation of the solid phase begins. This step is poorly understood because most of the theory developed for heterogeneous nucleation is applicable only for much slower processes, in part because material properties for highly supersaturated phases are unavailable. In many cases, the drying of microparticles produces particles with a non-equilibrium solid phase, which is undesirable for long term stability. Currently, this important step of the drying process is primarily studied experimentally[5] and by careful solid phase analysis of the final particles.[6] In the case of suspension or colloidal systems, an additional complication arises because the packing and assembly of nanoscale sub-structures need to be considered as well.

The last group of processes occurring during particle formation is related to changes in the mobility of the solid phase as the solvent content decreases. Initially the precipitated phases may be strongly plasticized, or ordered sub-structures may have enough mobility to re-arrange. Both of these effects can lead to plastic deformation of particles, manifesting itself in shell buckling or collapse of internal porous structures. Some attempts at describing these processes theoretically have been published[7], but in most cases experimental work is unavoidable, in particular careful ultramicroscopic analysis of whole or sectioned particles.[8]

Hybrid processes such as atmospheric spray freeze drying[9] have no evaporation phase, because droplets are frozen right after atomization and the water is removed mainly by sublimation. Here, new challenges are found in modelling the super-cooling and ice crystallization steps and in describing the desiccation of the freeze concentrate under near-collapse conditions. This technique is less developed but provides opportunities for particle design that are unavailable with standard spray drying.

Experimental Model Systems

Particle formation studies require a more controlled experimental environment than what is presented by a commercial spry dryer. The most idealised and arguably best-controlled model system is single particle levitation. Single droplets and dry particles in the respirable size range can be suspended acoustically, by light pressure, or via electrodynamic forces. It is advantageous to study individual particles in a gas phase that is well controlled and not influenced by the presence of the particle. Studies on single particles have contributed greatly to the understanding of aerosol microphysics[10], but they have two important limitations. First, it is difficult to study very fast processes in single particle traps because of the time it takes to trap a particle and to change the gas phase conditions. Second, only a single particle can be analysed at a time, precluding techniques that need a larger sample mass.

Droplet chain techniques partially address these limitations. Microdispensers can inject monodisperse microdroplets into a gas stream with extremely repeatable trajectories, in effect forming a chain of droplets whose temporal evolution can be measured along the length of the chain, making faster precipitation kinetics analytically available.[11] The dried particles can be collected and analysed by ultramicroscopy, but since the production rate of particles in this technique is limited to a few hundred Hertz, the amount of material produced is still insufficient for many analytical techniques.

Larger sample masses can be provided by a newly developed monodisperse spray dryer.[12] This instrument uses a vibrating orifice generator in place of the customary twin fluid nozzle of a standard size spray dryer. Some control over particle size and trajectory is lost, because the droplets from the vibrating orifice generator are closely spaced and need to be dispersed in a secondary gas nozzle. This dispersion leads to partial agglomeration, which is monitored with an in-process aerodynamic particle sizer. However, the resulting particles are still monodisperse and because the feed flow is much smaller than in a regular spray dryer, the drying gas conditions are largely unaffected by the presence of the droplets. This technique enables batch sizes of up to a gram of monodisperse test particles created in well described, homogeneous conditions. Further scale-up of monodisperse spray drying will require multiplexing of nozzles.

If larger batch sizes are necessary, e.g. to set up long term stability studies, moving to a bench top or pilot scale spray dryer will be at the expense of much of the control that the more idealised experimental test beds provide. However, it is still possible to improve on typical commercial systems by adding sensors to the dryer. This approach allows the development of process models,[13] which yield outlet conditions as a function of process parameters and describe the particles' exposure to temperature and humidity during the process. This rather minor effort is highly recommended, because it makes it feasible to correlate pilot scale process conditions with the controlled drying conditions of the model systems described above.

Application Examples

Some advanced particle designs have been successfully commercialized, for example the COPD medication Bevespi Aerosphere®, which is based on the co-suspension technology.[14] Others are in various stages of development. An area of particular interest is combination products, which after addition of suitable excipients may require the development of particles with many components. It has been shown that multi-component particle design benefits greatly from a systematic approach based on mechanistic understanding.[15] Another very active area is that of inhalable biologics. Particles that are suitable for this application provide glass stabilization for the biological and typically some dispersibility enhancement via a non-cohesive shell.[16] Such shells can be achieved by early crystallization of leucine, a process that can be described quite accurately by existing particle formation models.[17] Even sensitive biologicals, such as bacteriophages, can be processed with acceptable losses, stabilized for storage, and made dispersible for inhalation purposes.[18]

In summary, the mechanistic understanding of particle formation that has been gained over the last two decades is now put to use in the design of highly functional dosage forms. The advantages these particles hold in terms of storage stability and robustness will hopefully be of benefit to patients globally.

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