Pharmaceutical microparticles by spray-drying

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INTRODUCTION

Ideal drug delivery systems are supposed to target and to release the active molecule in the right body compartment at a desired rate for a specific disease. One of the strategies for developing those systems is the microencapsulation, which is defined as a technology of packaging solids, liquids or gaseous materials into microcarriers that are capable of releasing their contents at controlled rates under specific conditions. Conventional microencapsulation approaches usually require organic solvent, limiting both biomaterial design and applications for large molecular drugs and vaccine antigens.

Depending on the formulation and the application of the microparticulate drug carriers, several approaches have been used for their production, such as coacervation, emulsion solvent extraction, emulsion solvent evaporation, spray-drying and interfacial cross-linking polymerization. Briefly, the spray-drying method consists of the atomization of a liquid feed into a spray under hot air contact followed by the drying stage initiated by heat transfer. After the drying process, the dried particles are collected. On the other hand, interfacial cross-linking polymerization is a usual and long-established technique that requires the use of organic solvents and cross-linking agents, which may include toxic and harmful reagents. In fact, not only efficacy but also the safety is a key feature of drug delivery systems.

Drug instability and high costs associated with manufacture persist as key issues limiting development of controlled-release systems for large molecular therapeutics. Also, the encapsulation of lipophilic compounds into microparticles is often problematic from a technical point of view.

Spray drying and spray microencapsulation are one of the most widely spread technologies for particle generation in pharmaceutical technology (Verhing 2008) and in powder generation for drug delivery (Seville 2007).

In Spray drying the generation of small droplets is followed by solvent evaporation and the creation of a final powder product. The exact knowledge of the drying process, *i.e.* evaporation and transport processes inside the droplets, component distribution and skin formation, is of great interest for modeling and predicting product characteristics for given operating conditions.

Since experiments on real sprays are difficult to interpret and only integral information about an ensemble of droplets can be obtained, simple and idealized configurations considering single droplets are often preferred for investigation. Several techniques have been used for examining the drying of single droplets *e.g.* acoustic levitator, glass filament, nozzle and free falling droplets.

MATERIALS AND METHODS

Herein we focus on the mechanical methods generating micro- and nanoparticles. The strong originality of this study lies in the comparison of a new technology developed by Büchi, the so-called *Nano Spray Dryer B-90* (Figure 1) and the use of a conventional spray-drying technology (*Büchi B-290*) (Figure 2). The new technology allows to produce submicron particles, which is fundamentally new in the spray drying technology field.

Moreover, a traditional *spray drying process* is generally chosen as a technology to rapidly and efficiently transformation liquid substances in powders. The fastness of the process and thus the short drying time enables even drying of temperature-sensitive products without degradation. The resulting powder is a matrix system in the form of microparticles (*i.e.* microspheres), which can exhibit a spherical or hollowed morphology depending on the nature of the wall material used and on the operational drying conditions such as inlet temperature, solid concentration, gas flow rate or feed rate. The powder samples are generally heterogeneous and amorphous, the overall yields are around 70%.

The Nano Spray Dryer B-90 is based on a new spray drying concept. A whole schematic of the apparatus is illustrated in Figure 1. The drying gas enters from the top into the apparatus, heats-up to the setting inlet temperature, flows through the drying chamber, exits the spray dryer at the bottom outlet, and is fine filtered before leaving the instrument. The feed sample is fed by a pump to the spray head. As illustrated in the figure, the droplet generation is based on a piezoelectric driven actuator, vibrating a thin, perforated, stainless steel membrane in a small spray cap. The membrane (spray mesh) features an array of precise, micron-sized holes manufactured by laser drilling (4.0, 5.5 or 7.0 µm). The actuator is driven at ultrasonic frequency, causing the membrane to vibrate, ejecting millions of precisely sized droplets every second with very narrow distribution. These finest droplets are dried into solid particles which are

collected by electrostatic charging and are deflected to the collecting electrode.

The so-called *wall materials* used in this work relate to support materials for the spray drying process. Arabic gum (kindly provided by CNI Colloïdes Naturels International, Rouen, France), whey protein (kindly provided by DAVISCO Foods international Inc., USA), polyvinyl alcohol (PVA, from Sigma, Saint-Louis, USA), cleargum CO 03® and glucidex IT 12® (which are, respectively, modified starch and maltodextrin with DE 12, were kindly gifted by Roquette Frères, France) were successively used. Lipid nano-emulsions were chosen as a lipid model suspensions, with controllable size and polydispersity.

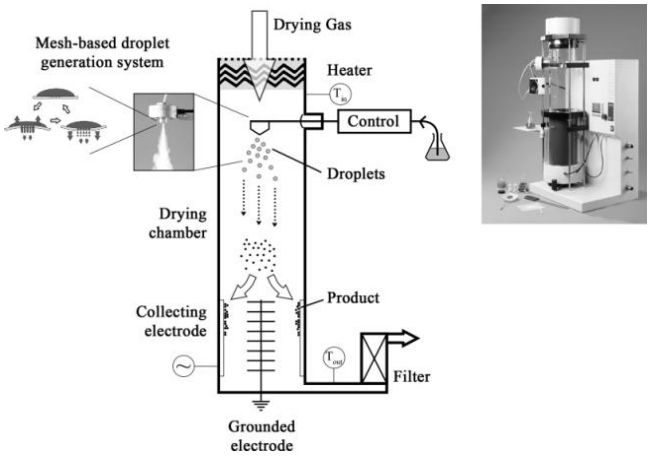

Figure 1: Schematic of the Büchi Nano Spray Dryer B-90

The size range of nano-emulsions was chosen a few orders of magnitudes smaller than the spray dried particles, that is, smaller than 100 nm. The formulation of nano-emulsions was performed according to a process published elsewhere (Anton, 2009). It is based on a low-energy spontaneous nano-emulsification mechanism, and results from the fast transfer of the hydrophilic surfactant from oil to the aqueous phase. Vitamin E acetate (Sigma) was used as model oily phase, Cremophor ELP® (BASF) as hydrophilic nonionic surfactant, and Ultrapure® water (MilliQ, Millipore) as aqueous phase. Firstly, the influence of the wall materials (polymeric nature) and the different experimental conditions (concentrations, influence of the powder location on the collecting cylinder) were studied by determining particle size, distribution, homogeneity, morphology, formulation yield, and general aspect of the samples. The second part of the work focused on the encapsulation of a model lipid dispersion (*i.e.* nano-emulsion formulated by a low-energy method) into dry submicron particles. Sample characterization was performed by scanning electron microscopy (SEM). Eventually, one aim of this study was also to grasp the potentials and possible applications and limits of this new technology.

RESULTS AND DISCUSSION

The particles formed with (a) arabic gum, (b) arabic gum encapsulating a nano-emulsion, (c) modified starch appear spherical, homogeneous, and example provided by pure arabic gum provide a log-normal size distribution centered around 600 nm, SD = 280 µm. Compared to particles produced with classical spray dryers (not shown in this abstract), the full potentials of this apparatus appears in terms of particle size, morphology, and homogeneity. The vibrating mesh spray technology generating the primary droplets finally appears to be the key for particle size reduction. However, the presence of surface active agents like nano-emulsion droplets of surfactants also plays a role in this result. Formulation yields were generally around 90%.

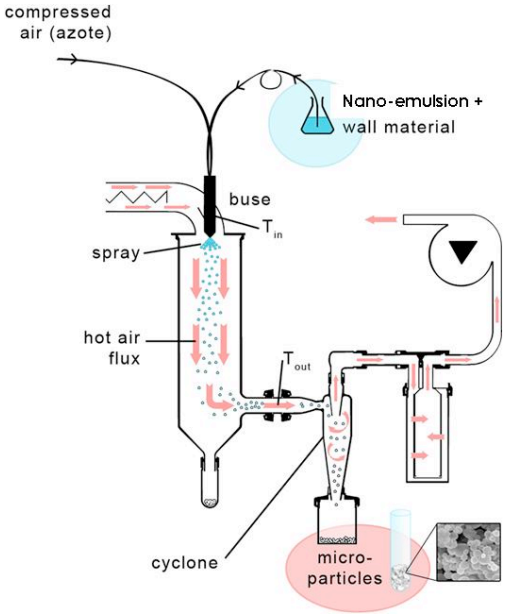

Figure 2: Schematic of the Büchi Nano Spray Dryer B-290

CONCLUSION

The Büchi Nano Spray Dryer B-90 appears to entirely fulfill the expected results of submicron particles. Preliminary results of encapsulated nano-emulsions and formulated nano-crystals raise a huge interest and offers new perspectives for novel pharmaceutical applications by spray drying.

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