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Commentary

Spray drying of proteins/peptides –why we should not fear the high temperature

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ABSTRACT

In the latest years spray drying has been adopted from other disciplines as a process to convert liquid proteins/peptides into more stable dry powder drug substances and products. By removing water, the molecular motion is reduced, which hence can improve storage stability and furthermore remove stringent and costly requirements for the storage temperature. Spray drying offers certain advantages above other drying methods with a more proven track record, amongst others time, cost, scale flexibility, continuous process and particle engineering. There is though still an on going hesitation for the full utilisation of spray drying for manufacturing of dry powder macromolecules in the industry due to the utilisation of heat in the process. For solvent evaporation, input energy is in the form of a hot drying gas around 100-200°C, which in the ears of a peptide/protein specialist may not sound like a recipe for success for such heat labile molecules. This presentation will however go through some common misconceptions about the spray drying process and discuss why spray drying holds a future in securing stable protein/peptide formulations. Furthermore we will present some concrete examples showing that we shouldn't fear the high temperature used in the process and even in some cases embrace it in order to produce high quality, stable dry powder proteins and peptides.

Keywords: Dry powder proteins; Heat labile molecules; Spray drying

INTRODUCTION

PThe high sensitivity of peptides and proteins to physicochemical stresses during processing and storage is the major hurdle against its pharmaceutical applications. Peptide-based drug for mulations are commonly prepared as solid dosage forms because more stability can be achieved in the solid rather than in the liquid state the most common methods to increase the stability of peptides and proteins are drying and the use of stabilizing excipients. So far, spray drying and freeze drying are the most popular methods of drying peptides and protein solutions in the Pharmaceutical industry. Other drying methods, like spray coating, spray freeze drying (SFD), and supercritical fluid technology and their different modifications, are mostly used on a small scale, especially for research purposes. The optimum choice of drying technique will depend mainly on the economics of drying and on the intended route of drug administration. Compared to freeze drying, spray drying is a faster and more economical, single step, drying method which can be designed as a continuous drying process. Spray drying is suitable for heat-sensitive materials, despite the high temperatures of the drying gas, owing to the cooling effect of the evaporating solvent which keeps the droplet temperature relatively low. Another advantage of spray drying technique is its ability to control the particle size and the morphology of the dried powder by varying the process parameters and the formulation factors. Moreover, spray dried powders are commonly prepared when the intended route of administration is via inhalation, so that this technique is of prime importance for pulmonary delivery of protein pharmaceuticals. However, low powder yield is still the major drawback in the development of spray dried pharmaceuticals because of small amounts of expensive active ingredients which are available after

Second by using a piezoelectric driven, vibrating membrane in the spray head. The final, dried particles are separated by the aid of an electrostatic particle collector with high product recovery. The main drawbacks of classical spray drying were the high sample volume required (minimum 50 mL), the low yield obtained (maximum 70%), and the big particle size (minimum2μM). However, by using the Nano Spray Dryer with its new advanced technology of the spray head, the heating system, and the electrostatic particle collector, the sample amount or volume can be as small as 200 mg or 2 mL, the final product yields increased up to 90%, the particle sizes decreased up to 300 nm with narrow size distribution,

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and, eventually, fast drying process (up to 150 ml/h) was attained. The major advantage of having nano size powder, especially in the field of proteomics and genomics, is to enhance the stability and therapeutic potential of these drugs to become more effective and less toxic.

Other essential optimization is to identify stabilizers, which are better suited to protect different proteins during the spray drying process with respect to the powder's inhalation properties, the storage stability and the shelf life of the final product. The major drawbacks are represented when the harsh processing steps render proteins or peptides more susceptible to physical and chemical instability through aggregation, denaturation, oxidation, and cleavage. Proteins are exposed to several shear stresses like shaking, pumping, and nozzle atomization during this spray drying process. Adsorption of proteins and peptides to different interfaces can result in unfolding of their structure that finally leads to the formation of aggregates. However, thermal stress is very important as proteins lose their native structure when exposed to sufficiently elevated temperatures and the native state of a protein is stable in a limited temperature range. Removal of water by dehydration processes, like spray drying, might lead to structural modification and protein denaturation. However, the pros and cons of Nano Spray Dryer on the level of nanoparticles formulation are quite different. The recovery of small particles intended for inhalation is significantly low usingthe classic spray dryer because of their poor separation in cyclone collectors owing to their low mass, a major drawback which was successfully overcome by recent developments and progress of nano spray drying technology as discussed earlier. At the nanoparticles' formulation level, the technology was successfully utilized for controlled delivery of peptides and proteins. These micro and nanoparticles can modify the release of the encapsulated peptides while retaining the biological activity. Combination of (HIP) method with organic spray drying and emulsion solvent diffusion method enhanced insulin encapsulation and release from PLGA nanoparticles. These nano particles enhanced the oral bioavailability of insulin thereby it was promising for oral insulin delivery. While PLGA nanoparticles encapsulating different drugs as peptides, proteins and small molecules can be produced with controlled physicochemical properties using Nano Spray Dryer, the ability to process small volumes to produce a high yield of small particles still represents the major advantage of this relatively new approach.