Abstract

Spray Freeze-Drying as a Solution to Continuous Manufacturing for Preserving Macromolecules

Many pharmaceutical and food products are not sufficiently stable in aqueous solution for long periods of time and may undergo various chemical and physical degradation reactions. Removing the solvent by drying techniques to convert the material into a solid state is one of the safe and effective mechanisms to promote long-term stability. The low temperature vacuum drying provided by freeze-drying is a widely used process for drying formulations containing bio- products, as they are thermolabile substances. The freeze-drying process is well researched and proven to be suitable for many products. However, it still relies on batch production despite the potential advantages of continuous processing such as increasing output and efficiency, reducing costs and environmental footprints, accelerating production, and responding to market demand for scale-up.

Among the various drying techniques available, spray freeze-drying (SFD) is the research interest of this thesis as a relatively new drying method to convert bio-derived products into solid particles. The SFD method consists of three steps: 1) generation of droplets by spraying solution with an atomizer 2) freezing of the droplets in a cryogenic environment, usually achieved with liquid nitrogen 3) drying of the particles by freeze-drying cycle. Therefore, thermolabile bio-products can be carefully dried at low temperatures to produce very light, highly porous and spherical particles. Besides being a suitable process for heat sensitive substances, SFD has the potential to be applied as a continuous manufacturing where the development of technologies and integration of continuous processes is a hot topic in the pharmaceutical industry today. However, the difficulty is not so much to obtain dry spherical particles; The difficulty arises as the transition from batch to continuous production requires a fundamental understanding of SFD principles by explaining each step of the process from atomization to drying. Not enough literature exists on product development and process design of SFD process. In addition, there is a lack of experience in the manufacturing technique within the industry in line with specifications. There are many factors that may cause a bio-product to have different physical characteristics of the dried powder and lose its activity during processing. Controlling powder properties such as particle size, size distribution, morphology, bulk density and moisture content is crucial for many aspects of bio-product processing. In this thesis, SFD, which may allow the continuous production of dry particles, is investigated to understand its ability to control these characteristics accurately.

After giving a brief overview of the recent application of SFD processing for pharmaceuticals and food materials, particle production using SFD was investigated to better understand the impact of formulation and processing conditions on the characteristics of the final powder. Since there was no prior experience in this field in the Department of Applied Science and Technology, PoliTo, the study was started by characterization of microsphere particles obtained by SFD process. The first step in SFD, the atomization step, predominantly determines the final particle characteristics as

morphology and size of particles. Therefore, the impact of different solid concentration of formulations consisting of sucrose and mannitol and their processing under different atomization conditions on the final product was investigated. This research was followed by the investigation of the effect of the SFD process in the production of protein-based formulations, as proteins are the main building blocks of many biopharmaceuticals. Since SFD is a combination of three steps, atomization, spray freezing and freeze-drying, the effect of each step on the activity of proteins was investigated, using lactate dehydrogenase and myoglobin as model proteins. The loss of activity of proteins during SFD may depend not only on the process conditions but also on the protein type and the correct formulations. For this reason, different type of proteins and excipients were selected.

On the other hand, the lack of high-quality experimental data due to the complex nature of the process and the difficulty in making detailed measurements has recently drawn attention to the development of mathematical models. Although several models have been proposed in the past, they all presented various flaws and fell short of describing process behavior. The literature also reveals that the models published so far are based on previously published experiments, and none of the models are based on real experimental data. Therefore, a new model based on the concept of a dispersed interface was proposed using Computational Fluid Dynamics (CFD) and COMSOL Multiphysics to more accurately describe the process and drying behavior of spray-frozen particles arranged in a packed bed.

The developed model has proven that the internal temperature of the spray-frozen particle beds is incredibly sensitive to the internal structure of single particles. Temperature measurements of the packed bed of spray-frozen particles are particularly difficult when using common thermocouples, as they are in contact with different materials at the same time, e.g., solid particles and water vapor. While measuring the internal temperature of single particles is difficult due to their small size, the use of infrared (IR) thermography can give an accurate reading of the temperature of packed bed of spray-frozen particles compared to thermocouples. The application of an IR camera for the first time in the literature to monitor the primary drying of packed bed of spray-frozen particles allowed the sublimation interface to be detected. Since sublimation is an endothermic process, the sublimation interface was monitored by following the axial minimum temperature of the packed bed during primary drying. In addition, the IR data helped to estimate the end of primary drying more accurately and the temperature measurement of the packed bed compared to thermocouples.

Finally, SFD was evaluated for its use in the food industry, where various approaches have been applied to extend the shelf life of commercial products containing bioactive ingredients. Encapsulation, which is very important for the food industry, plays an important role in maintaining and controlling the structure of an active ingredient. The study aimed to compare the effect of SFD, freeze-drying and quench freeze-drying in liquid nitrogen on the stability of encapsulated omega-3 fatty acid. Lipid oxidation was monitored via the analysis of dynamic light scattering for the comparison of different drying processes.

Overall, the aim of the whole study was to prove that SFD could be a promising technique as an alternative to freeze-drying in the production of heat sensitive bioproducts for both the pharmaceutical and food industries.