Abstract

The use of therapeutic proteins is considered highly promising in the pharmaceutical field. However, instabilities of protein-based therapeutics during manufacturing and long-term storage are the main challenges. Stress factors that occur during processing and storage, e.g., temperature, interfaces, and shearing or stirring, can accelerate unwanted degradation of proteins.

To stabilize therapeutic proteins against degradation, the addition of stabilizing excipients and freeze-drying are commonly used strategies. Recently, the spray-drying process has attracted interest as an alternative to freeze drying to formulate and manufacture protein-based therapeutics. In the spray-drying process, a feed solution containing the protein of interest and excipients is converted into solid powder; this approach has multiple positive technical features such as fast processing, lower energy consumption, possibilities for particle engineering and the potential for continuous manufacturing. The presence of a co-solvent in the feed can influence the particle formation process and dramatically impact the resulting particle properties. Furthermore, handling of the powder and product performance, e.g., aerosolization of dry powders, may be affected.

This PhD project was aimed at exploring the potential of using ethanol as a co-solvent in the feed solution for spray drying of protein formulations. The effect of the addition of ethanol in the feed solution on both the aerosolization performance and the stability (i.e., conformational and chemical stability) of model proteins (lysozyme and insulin) were investigated in this project. In addition, some formulation strategies to enhance the stability of the spray-dried protein formulations were attempted. To this end, advanced analytical techniques including scanning electron microscope, Fourier transform infrared spectroscopy, circular dichroism, high performance liquid chromatography, thermogravimetric analyzer, etc. were utilized to characterize the resulting spray-dried protein powders.

Morphology modification and improved aerosol performance of spray-dried lysozyme powders were observed when ethanol was added in the feed solutions as a co-solvent. The addition of ethanol in aqueous feed did not result in detectable conformational change in the spray-dried lysozyme. However, the enzymatic activity of spray-dried lysozyme was reduced when compared to the untreated raw material. Nevertheless, the enzymatic activity could be preserved
by an addition of stabilizing additives, such as trehalose, Tween 20 to the feed solution or adjusting the pH of the feed solution. The addition of 20% (w/w) of ethanol to the spray-drying feed solution did not dramatically compromise the protein structure and bioactivity, and therefore this modification would have potential for particle engineering purposes.

When human insulin was used as a model protein, similar morphology change in spray-dried insulin powders was observed with an addition of ethanol to the aqueous feed solutions. However, an addition of ethanol to aqueous feed solutions seemed to promote more chemical degradation of human insulin. This might be attributed to the presence of ethanol promoted monomeric state of insulin in the feed solution as compared to in the pure water feed, which might be more prone to the stresses in the spray drying process. However, the addition of excipients such as phenol in the feed solution to maintain the hexameric state of human insulin did not effectively prevent chemical degradation of human insulin upon spray drying.

All in all, this study demonstrated the pros and cons of an addition of organic solvent in the aqueous feed for spray drying of protein formulations. The addition of organic solvent to the feed could provide increased possibility of particle engineering. Nevertheless, certain efforts will be needed to circumvent the negative impact of organic solvent on protein stability.