Finally, the arguably most significant disadvantage of spray-drying compared to freeze-drying is the process efficiency. Freeze-drying results in very little loss during drying, whereas yield is a persistent drawback with spray-drying, particularly with small particles, which may not efficiently deposit in the cyclone [37]. The choice of the optimal drying method is largely determined by the tolerable operating temperature for a specific biopharmaceutical and the final dosage form.

Challenges Specific to Spray-Dried Biopharmaceuticals

The benefits of spray-drying for biopharmaceuticals are the same as the overall benefits of spray-dried formulations in general, namely, it is a one-step process, scalable to the industrial level, less time consuming than other drying methods, and offers tight control of particle properties. Formulating proteins and other biologics remains a challenge in pharmaceutical research due to the range of possible chemical and physical degradations to overcome—deamidation, oxidation, hydrolysis, disulfide bond shuffling, conformational changes, adsorption to surfaces, denaturation, precipitation, and aggregation [54]. Because of these sensitivities, formulating biopharmaceuticals is accompanied with limitations on tolerable operating temperatures, pressures, and environments. The ability to tightly control the morphology of the resultant particles, the ability to tune the size of the particles, the ease of incorporation of excipients for the controlled release of compounds, and the final product in a dried state which extends the storage life of the product all contribute to the extensive use of spray-drying in the formulation of biopharmaceuticals.

However, there are several sources of stress in the spray-drying process which are particularly important due to their possible negative effects on the stability of biopharmaceuticals—high pressure, high shear, atomization pressures, temperature, and dehydration. Without the use of stabilizing excipients such as sugars, amino acids, and surfactants, spray-drying can cause thermal degradation, conformational changes, and aggregation. Understanding the interactions between excipients and biomolecules and the excipient(s)' role in stabilization helps to determine optimal excipient concentrations to maximize biomolecule activity. Specifically focusing on protein stabilization, different excipients protect a protein from different sources of destabilization. Several stabilization mechanisms have been put forward to explain the effects of stabilizing excipients and the causes of destabilization in the spray-drying process. Specifically, protein aggregation, and subsequent inactivation and structural changes, have been linked to (1) dehydration during the drying process and (2) interaction with the air/liquid interface during atomization.

Proteins can tolerate shear and shear rates as high as 10^7 and 10^5 s^{-1}, respectively, in liquid medium without protein aggregation and activity loss, though they may still be subject to conformational changes as assessed in recombinant human growth hormone (rhGH) and recombinant human deoxyribonuclease (rhDNase) at high shear rates [55]. Amphiphilic proteins will aggregate at the surface of interfaces, such as air–liquid interfaces, exposing their hydrophobic regions towards