Towards more stable drug delivery systems: Drying of RNA-containing lipid nanoparticles

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The pharmaceutical application of ribonucleic acid (RNA) delivered via lipid nanoparticles (LNPs) has gained significant interest in recent years. One of the biggest challenges still remaining with this drug delivery system is the instability of both RNA and lipid [1], resulting in the need for ultralow temperatures during transport and storage. One possible way of overcoming this challenge is the removal of free water from the liquid formulation to gain a dry form. This holds the advantage of reducing the molecular mobility and increasing the stability, a concept well established for different sensitive biologic molecules. However, the removal of water also exposes the lipid nanoparticles and RNA to different stresses, which can vary greatly depending on the drying method used. We therefore evaluate different drying methods to identify the respective influences of various stresses on the product.

As a model formulation, Comirnaty KP.2 (BioNTech) was used as mRNA-containing LNPs and 20 %(w/w) sucrose was added to the liquid formulation as matrix material for drying. The main read out parameters were LNP size after reconstitution and RNA content after drying. In this study, we used freeze drying, spray drying and freeze spray drying. In freeze drying low temperature and low pressure lead to a sublimation of the water resulting in a dry porous cake, which can be reconstituted directly in the freeze drying vial by adding water prior to injection. Stresses during this process include thermal and ice-liquid interfacial stress during freezing and consequently osmotic pressure due to a concentration increase in the solution. In spray drying, the formulation is atomized from a nozzle into a stream of hot gas. This results in the drying of single droplets and ideally a free-flowing, dry powder. The stresses involved in this process are shear stress caused by droplet disruption at the nozzle and thermal stress caused by drying with heated gas.

When drying LNPs, the resulting particle size is bigger than prior to dying (see Fig. 1). This was observed before and can partly be attributed to the formation of blebs. These are protrusions formed on LNPs due to stresses enacted on them resulting in a loss of the ideal spherical shape [2]. For each drying process, the main process parameters were systematically varied to gain understanding of the acting stresses. Lower freezing temperature with lower cryo-concentration stress showed a lower LNP size increase. For LNP size after spray drying, a dependency on temperature and nozzle size could be shown as these parameters govern drying of single droplets. As drying results in a solid form, it opens up alternatives to vaccine application via injection. For example, administration of the drug delivery system via the pulmonary route by powder inhalation [3]. Therefore, spray dried particles were also analyzed regarding particle size. As freeze drying proved to work well for keeping both LNPs and RNA intact, the process was adapted by freezing single droplets in liquid nitrogen (freeze spray drying) as well as milling freeze dried cakes to result in single particles for inhalation. Using freeze spray drying, RNA is more sensitive to shear than the LNPs are, as the RNA content diminished with a reduction in nozzle size while the LNP size stayed similar.

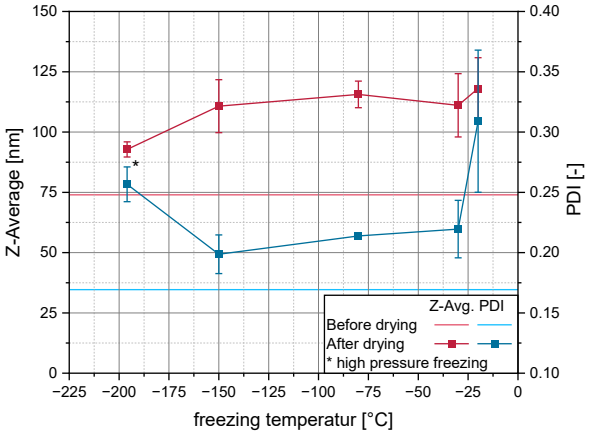

Fig. 1: Particle size of freeze dried LNPs after freezing at different temperatures

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