



Cover story

Thin-film freeze-drying for lyophilization of vaccines



Many currently available vaccines contain aluminum salts as adjuvants to increase the body's immune responses to the vaccines. Vaccines that use aluminum salts as an adjuvant are physical suspensions of aluminum salt microparticles adsorbed with antigens. A major limitation of those vaccines is that they are sensitive to freezing conditions and are too fragile to remain stable at ambient temperatures. This requires vaccines to be maintained in a cold chain (2–8 °C) and not to be exposed to freezing temperatures during transport or storage. Freezing causes irreversible aggregation of microparticles that inactivates the vaccines. The cold-chain accounts for a large portion of the financial costs of vaccination [1], and yet temperature excursions during vaccine shipment and storage results in inactive vaccines or less than optimal efficacy. Clearly, there is a need to overcome this limitation. It is thought that converting vaccines containing aluminum salts from liquid suspension to dry powder may render the vaccines insensitive to freezing temperatures and allow storage at ambient temperatures.

In this issue, the team of investigators led by Professors Zhengrong Cui and Robert O. Williams III presents a method of freeze-drying vaccines that contain aluminum salts without causing particle aggregation or decreasing the immunogenicity following reconstitution [2]. They utilized a thin-film rapid freezing process. Liquid droplets are allowed to fall from a given height to a cooled solid substrate so that they can spread and freeze on the time scale of 70–1000 ms [3]. The resultant frozen films are then lyophilized. Thin-film freezing has been used to form powders of poorly water soluble drugs and proteins. Professors Cui and Williams and their groups tested the feasibility of using thin-film freezing to lyophilize vaccines containing aluminum salts. The Cui–Williams group used six different vaccines, including vaccines prepared with a model antigen in their laboratories and commercially available veterinary and human vaccines such as tetanus vaccine, human hepatitis B vaccine, and human papillomavirus vaccine. All vaccines are adjuvanted with various types of aluminum salts, such as aluminum hydroxide, aluminum phosphate, potassium aluminum sulfate, and amorphous aluminum hydroxyphosphate sulfate. The Cui–Williams team showed that vaccines subjected to thin-film freezing followed by lyophilization did not cause particle aggregation after reconstitution. Moreover, the team showed in mouse models that such vaccines did not decrease the immunogenicity of the vaccines tested. The team also showed that subjecting the vaccine powder to multiple cycles of freezing-and-thawing did not cause particle aggregation upon reconstitution [2].

It appears that trehalose (2%, w/v) added into the vaccines formed a powder with a high glass transition temperature after thin-film freeze drying. The trehalose surrounding the antigen-adsorbed aluminum salt particles is thought to prevent the particles from interacting with

one another during the thin-film freeze drying process and inhibit their aggregation upon reconstitution. It was unexpected that the thin-film freezing could be used to freeze-dry vaccines containing relatively high concentrations of aluminum salts and with only 2% trehalose as a cryoprotectant. Previously, spray freeze-drying was used to lyophilize vaccines containing aluminum salts, but the cooling rates during spray freezing might have been up to 100-fold higher [3]. Furthermore, higher levels of excipient(s) and relatively lower levels of aluminum salts were used. The Cui–Williams group speculates that the spread film formed by the relatively smaller area of the air–liquid interface of the falling droplets may have contributed to the improved stability of the vaccines. The proposed hypothesis is reasonable, but more studies must be carried out to confirm it. In addition, the immunogenicity of vaccines made by thin-film freeze-drying after being subjected to freezing or storage at ambient temperatures must be evaluated to ensure that the vaccine powder maintains its efficacy. The importance of the study of the Cui–Williams team is that it provides a possibility of developing vaccine formulations that can eliminate the cold chain. In fact, such new vaccine formulations are essential in distributing vaccines, especially in underdeveloped countries where vaccines are greatly needed. The drug delivery field needs more research like the work by the Cui–Williams team to make real differences in our daily life.

References

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