Feasibility Study for Continuous Freeze-drying

Minami Yoshikata[1]; Hideki Ito[2]; Jumpei Nagata[3]; Sho Kawatsu[4]

[1] Astellas Pharm Inc., 180, Ozumi, Yaizu-shi, Shizuoka, minami.yoshikata@astellas.com, +81-80-2176-3260

[2] Astellas Pharm Inc., 180, Ozumi, Yaizu-shi, Shizuoka, hideki.ito@astellas.com

[3] Astellas Pharm Inc., 180, Ozumi, Yaizu-shi, Shizuoka, jumpei.nagata@astellas.com

[4] Astellas Pharm Inc., 180, Ozumi, Yaizu-shi, Shizuoka, sho.kawatsu@astellas.com

INTRODUCTION

Lyophilization (freeze-drying) is widely used as an effective tool to improve stability of drug products during their shelf life. Lyophilization begins with freezing of drug solution, followed by sublimation under vacuum to remove the water. As a result, lyophilized products can be stored for long time with maintaining quality and efficacy of active ingredients.

However, there are several issues with conventional batch freeze-drying (Batch FD) technology.

1. Processing time: It often takes long time from loading filled products to finishing drying process and would be over a week if containers have large filled volume. Additionally, variety in quality can occur even within the same lot due to differences in thermal conductivity at various locations in a lyophilizer.
2. Foreign matter detection: It is difficult to detect foreign matters in finished products because they are often hidden within lyophilized cake of products.
3. Reconstitution time: Lyophilization requires additional effort in clinic to prepare dosing by reconstitution of lyophilized products, which takes long time due to thickness of lyophilized cake and reduces usability and flexibility for healthcare providers.

Spin-freezing is one novel technology to solve these issues that consist of freezing and drying process while rotating containers, resulting in thin layer of lyophilized cake on inner wall of containers. This technology enables us to reduce processing time by expanding surface area of frozen content and delivering required energy efficiently as well as easily detect foreign matters because there is less space for them to avoid detection. Also, reconstitution time is significantly reduced due to large surface area and thin layer of lyophilized cake. Spin-freezing technology can be leveraged to continuous freeze-drying (Continuous FD) for larger production scale. Feasibility study for Continuous FD using RheaLyo™ Mono Freeze-Dryer (Fig.1) as single vial unit (SVU) from RheaVita BV was conducted to demonstrate its benefits on the common issues seen in Batch FD.

Figure 1. Image of RheaLyo™ Mono Freeze-Dryer

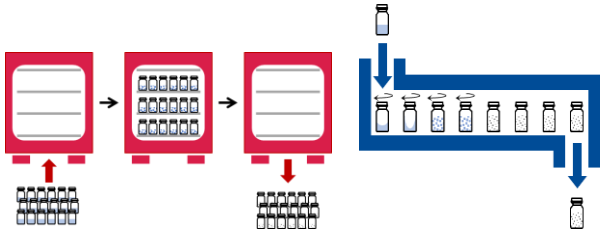


Figure 2. Schematic diagram of the differences between Batch FD (left) and Continuous FD (right)

An image of the continuous FD process is shown below (Fig.3). In the freezing step, super cooled gas is sprayed while the vial is rotated. For drying, the vial is heated by an IR heater and the vial temperature is monitored using an IR pyrometer.

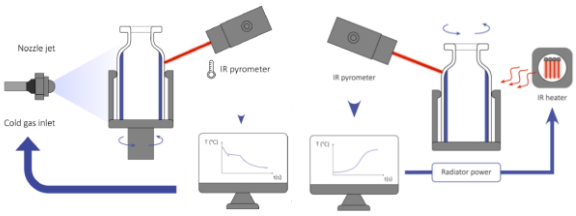


Figure 3. Schematic diagram of the process of Continuous FD

METHODS

To produce samples for the study, SVU and a conventional batch freeze dryer were used to compare Batch FD and Continuous FD. Samples were produced using biologics and its placebo and evaluated stability, detectability of foreign matters, reconstitution time and processing time.

RESULTS

Stability

The stability of antibody A in the lyophilized samples was evaluated at 40˚C for 2 months. The result shows the stability of the Continuous FD samples was comparable to that of Batch FD samples.

Table 1. Stability of antibody A in the lyophilized products

Type of FD		Batch FD		Continuous FD	
Storage condition		Initial	40˚C2M	Initial	40˚C2M
SEC (%) (n=2)	Monomer	98.7	98.7	98.4	98.4
	LMW	0.6	0.6	0.6	0.6
	HMW	0.8	1.1	0.8	1.0

LMW: Low Molecular weight, HMW: High Molecular Weight

Foreign matters

Lyophilized placebo samples with spiked foreign matters (hairs, fiber, etc.) were prepared using SVU. As a result, the foreign matters were easily detected by visual inspection, because a thin layer was formed along the inner wall and the foreign matters were pushed out onto outer surface of cake. This will be easily detected even by automatic inspection machines.

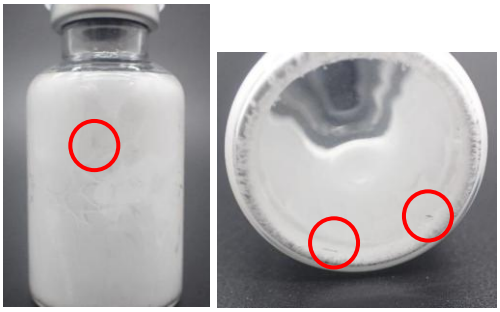
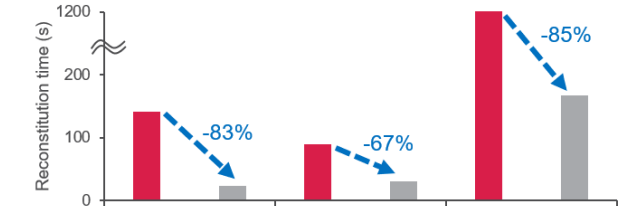


Figure 4. Lyophilized sample by SVU with spiked foreign matters (hairs)

Reconstitution time

Reconstitution time of Continuous FD samples and Batch FD samples were compared. That of Continuous FD samples was significantly shorter than that of Batch FD samples, regardless of the modality of the drug.



Modality	Ab	Bi-specific Ab	PROTAC
Vial size	20 mL	3 mL	2R
Fill volume	5.25 mL	1.2 mL	1 mL

Ab: Antibody, PROTAC: Proteolysis Targeting Chimera

Figure 5. Reconstitution time of Continuous FD and Batch FD samples

Processing time

Processing time per vial of Continuous FD samples and Batch FD samples were calculated based on results in lab-scale. The processing time per vial for Continuous FD samples was significantly reduced compared to Batch FD samples. This will lead to a significant reduction in the process evaluation period at lab-scale and a reduction in processing time at manufacturing scale.

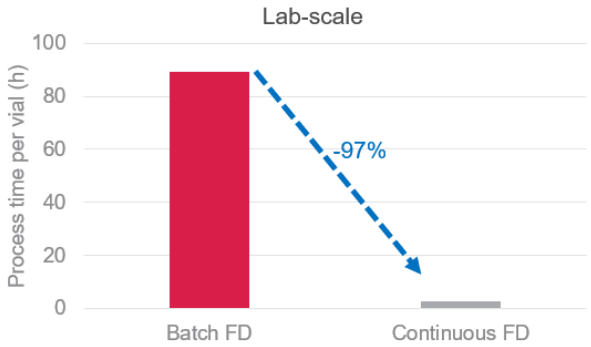


Figure 6. Processing time of Continuous FD and Batch FD

CONCLUSION

The feasibility study of Continuous FD by Spin-freezing was conducted. It was shown that Continuous FD is useful to solve the issues of Batch FD (processing time, detectability of foreign matters, reconstitution time etc.) without any change of the stability. These findings help to improve the usability of clinical staffs. Additionally, it helps to reduce production costs by decreasing processing time.

REFERENCES

1. Schaal, Z., De Meyer, L., Van Bockstal, P.-J. & Corver, J. Optimization of continuous spin-freeze-drying: The role of spin-freezing on quality attributes and drying efficiency of a model peptide formulation. Int. J. Pharm. 646, 123456 (2024).