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Homogeneous Heat Transfer During Freeze-Drying Using Cyclic Olefin Polymer Vials

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ABSTRACT

In pharmaceutical freeze-drying processes, batch homogeneity is an important quality attribute. In this context, the edge-vial-effect is a challenging phenomenon. Shortly, this effect describes that vials at the edges of the shelf dry faster and at a higher temperature compared to vials in the middle of the shelf. Studies by Ehlers et al. revealed that this effect mainly origins from the number of neighbor vials cooling each other, which is reduced for vials in corners and edges compared to vials in the middle. Due to the reduced heat transfer in cyclic olefin polymer (COP) vials, the adverse edge-vial-effect should be greatly reduced allowing a better batch uniformity. In this focused study, glass and COP vials are compared regarding this effect on a fully loaded shelf. A reference experiment with vials placed at distance using a specially designed frame is presented as well.

Introduction

Freeze-drying is a suitable and gentle method to desiccate biotherapeutic formulations to increase their shelf life.[1–3] The process must be designed carefully to be as fast as possible but moderate enough to avoid collapse of the drying matrix.[1,4] Furthermore, batch homogeneity must be ensured. Thus, the edge-vial-effect remains to be a challenge.[5] This long-known effect leads to a difference in temperature distribution among the vials during the drying process. Studies of Ehlers et al. revealed that this effect is mainly driven by the amount of neighbour vials cooling each other, which is reduced for vials at the edge or corner of a loaded freeze-dryer shelf.[6] By isolating the vials from each other or increasing their distance on the shelf, the neighbour-vial-effect can be strongly reduced. However, the number of vials per shelf is lowered when the vials cannot be packed closely together and this is not at all desired as it makes lyophilized products even more expensive.

An option to isolate the vials from each other could be to use the properties of the material of the vials. Vials made of cyclic-olefin-polymer (COP) are more isolating than glass vials[7] and are readily available on the market.[8] More properties of COP vials and their usability compared to glass vials can be found elsewhere.[9–11] Due to the different thermal properties of the COP vials, the neighbor-vial-effect could be reduced even if the vials are closely packed on the shelves and have direct contact to each other. To investigate this theory, a full loaded shelf of glass vials and COP vials is processed and compared in this study. The products are visually inspected, and the distribution of residual moisture (r.m.) is measured. Furthermore, a reference experiment with distanced vials is performed with a specially designed frame.

Material & Methods

Preparation of the Formulation

A placebo formulation used was composed of 4.6 % sucrose (w/v) (Sigma-Aldrich, Steinheim, Germany), 0.23 % L-histidine (w/v) (Merck kGaA, Darmstadt, Germany) and 0.01 % polysorbate 80 (PS80) (Croda Inc, Princeton, NJ, USA) according to the work of Ehlers et al.[6,12] The pH was adjusted to the final value of 6.0 using HCl 0.1 M (Bernd Kraft GmbH, Duisburg, Germany). The formulation was filtered with a 0.22 μM filter before use.

Glass- and Cyclic Olefin Polymer Vials (COP-Vials)

Cyclic olefin polymer 2R vials (COP Monolayer, Gerresheimer AG, Boleslawiec S.A., Poland) and borosilicate glass 2R vials (MGlas AG, Münnerstadt, Germany) were used. Both have a nominal capacity of 2 mL and a minor neck of 13 mm.

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Table 1
Freeze-drying protocol.

	Step No.	Time [hh:mm]	Temperature Shelf [°C]	Vacuum [mBar]
1	**Loading**	0:01	20	1000.00
2	**Freezing**	0:20	0	1000.00
3	**Freezing**	2:10	0	1000.00
4	**Freezing**	0:45	−45	1000.00
5	**Freezing**	2:30	−45	0.07
6	**Prim. Dry.**	0:15	−45	0.07
7	**Prim. Dry.**	0:20	−25	0.07
8	**Prim. Dry.**	50:00	−25	0.07
9	**Prim. Dry.**	0:50	25	0.07
10	**Sec. Dry.**	0:15	25	0.07
11	**Sec. Dry.**	5:00	25	0.07
12	**Sec. Dry.**	0:20	5	0.07

Lyostoppers

Stoppers with a diameter of 13 mm (Flurotec® laminated rubber stoppers, West Pharmaceutical Services, Inc, Exton, PA, USA) were used.

Freeze-Drying Process

Freeze-drying was performed with an Epsilon 2–6D laboratory scale freeze-dryer (Martin Christ, Osterode am Harz, Germany. A protocol based on Ehlers and coworkers was used (Table 1).[6,12]

Visual Inspection of the Freeze-Dried Products

All the vials were inspected visually. Pictures from the cake and the bottom of the vials were taken.

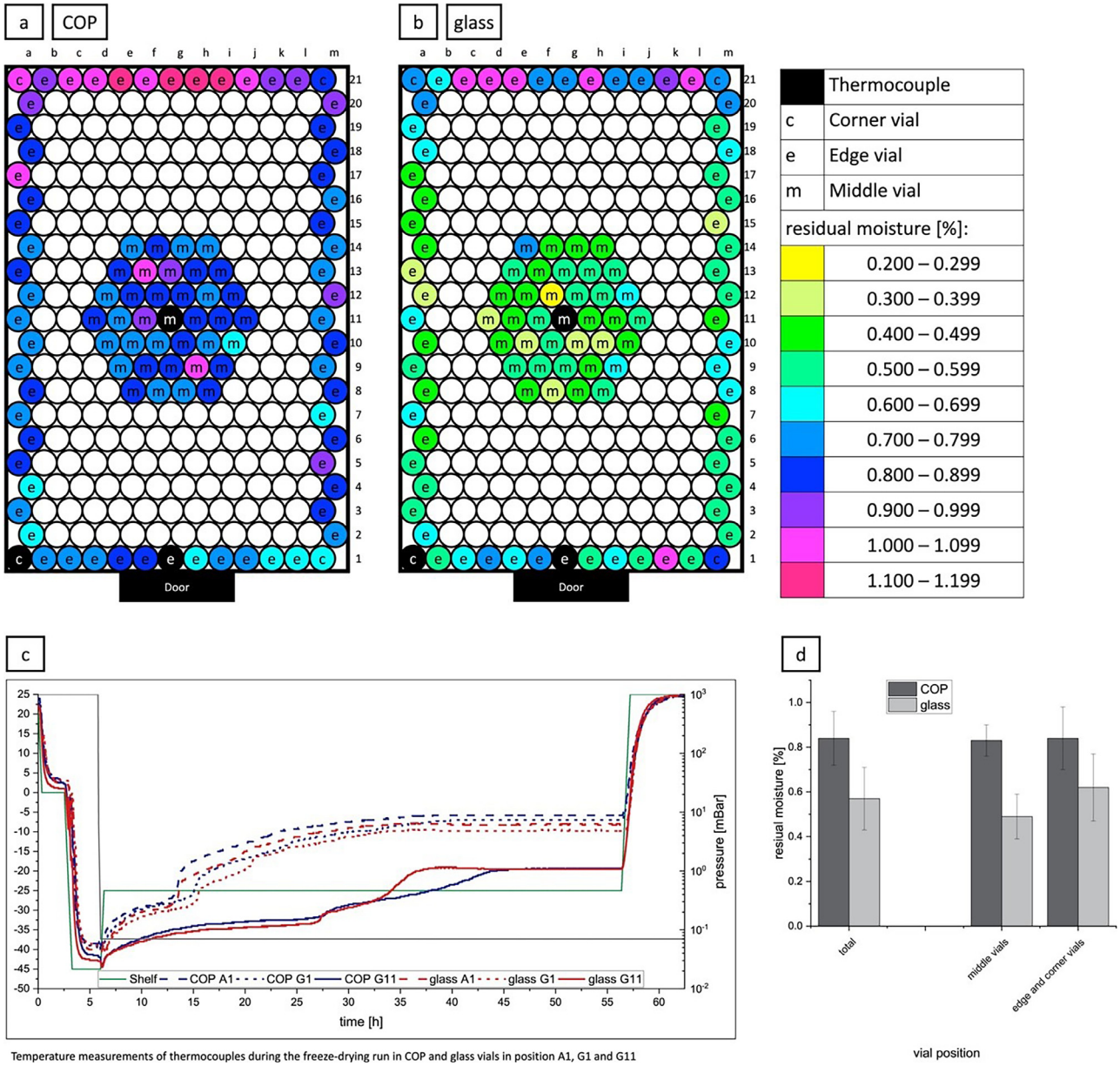

Figure 1. Summarized results of the placebo properties. Distribution of residual moisture in COP Vials (a) and in glass vials (b). Process results with trending of the temperature sensors (c) and summarized residual moisture values (d).

Headspace Karl Fischer Titration

The residual moisture level was determined by Karl Fischer titration method using an Aqua 40.00 Vario plus, ECH Elektrochemie Halle GmbH, Halle, Germany. The samples were placed in an oven at 100° C to extract the water. The water was transferred to the coulometric titration cell. Relative moisture content was calculated based on the weight of the sample (w/w). Before sample analysis, equipment performance was verified by measuring the Aquastar® water standard oven 1 % (Merck KGaA, Darmstadt, Germany) in triplicate.

Results

Fig. 1 summarizes the results of the freeze-drying run with the fully loaded shelves.

Residual moisture. Overall, the r.m. is expectedly higher for COP vials (0.84 ± 0.12%) compared to glass vials (0.57 ± 0.14%). If the r.m. is compared separately between middle vials (MV) with edge and corner vials (EV), a uniform distribution is found in COP vials where the r.m. for MV is 0.83 ± 0.07% and for EV 0.84 ± 0.14%. In contrast, glass vials show inhomogeneities with the r.m. in MV being 0.49 ± 0.10% and in EV 0.62 ± 0.15% (Fig. 1*a* + *b*).

Evaluation of the thermocouples. The course of the temperature sensors in Fig. 1c show that independent of the material, corner vials dry as fastest, followed by edge vials and middle vials needed the longest. Comparing COP with glass, it can be seen, that the temperature of the product increases more continuously in COP vials. Especially when the middle vials are compared, a steady temperature ramp can be seen for COP vials in contrast to the glass vials where distinct jumps in temperature are observable.

Visual inspection. The visual inspection of the vials clearly shows elegant cakes in the COP vials whereas shrinkage is evident in nearly every glass vial (Fig. 2a). Also, the number of neighbouring vials can be seen in the shape of the hexagonal cake shrinkage in glass vials (Fig. 2b).

Freeze-drying with a frame. Also with the frame, the r.m. in COP vials is higher (0.87 ± 0.06%) than in glass vials (0.70 ± 0.06%). However, now in the glass vials and COP vials the same uniformity in r.m. is reached, with 0.69 ± 0.06% for MV and 0.70 ± 0.06% for EV.

Discussion

The increased r.m. in COP vials compared to glass vials is not surprising. One factor that determines the speed of the sublimation in primary drying, is the thermal energy provided by the shelves.[13] With COP vials behaving more isolating, it takes more time until the heat of the shelves reaches the ice and sublimation in COP vials is slowed down. On the other hand, this can be beneficial for a uniform heat transfer.

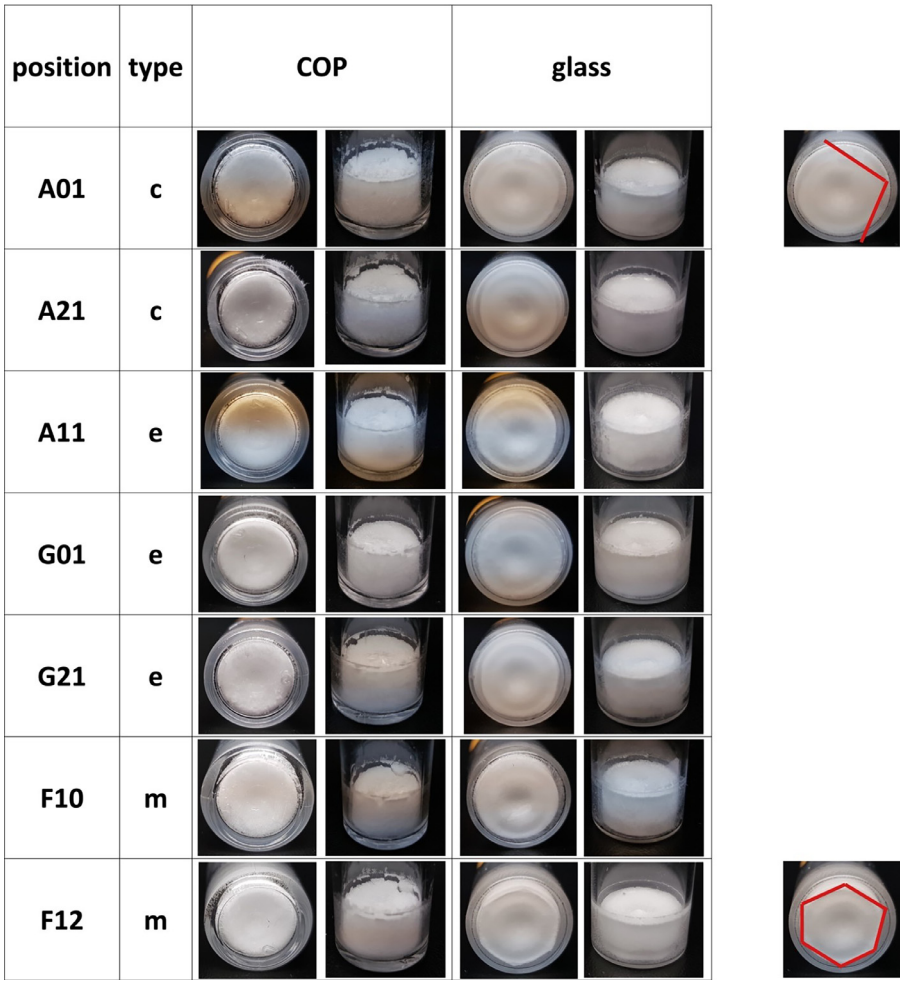

Figure 2. Macroscopic cake appearance of corresponding partners of COP and glass vials. *c* = corner vial, *m* = middle vial and *e* = edge vial. The first picture shows the bottom of the cake, the right picture the full cake. The bottom of the position A01 and F12 for glass vials is copied and the shrinkage caused by the neighbouring vials is marked with red lines for better visibility.

The comparison between MV and EV on the fully loaded shelf shows that a much better uniformity is reached in COP vials. Taking the relative standard deviation (RSD) into account, it can be calculated that the RSD for the r.m. for COP vials is 14.13% whereas it is much higher for glass vials with 25.16%. Furthermore, a uniformity factor (UF) can be calculated by dividing the values of the EV with the values of the MV. An UF = 1 would mean the same r.m. in every vial; the results are UF_{COP} = 0.98 and UF_{glass} = 0.80. Thus, the theory of an increased vial to vial homogeneity by the use of COP vials can be proven in practice.

Also, the neighbouring-vial-effect can be prevented with the use of COP vials. No shrinkage can be observed in the freeze-dried cakes obtained in COP vials, confirming the theory, that cake shrinkage is driven by neighboring products that cool each other.[6]

The control experiment with the frame aligns with the results of the fully loaded shelves (Fig. 3). With the higher distance between the vials and without direct contact, the now isolated glass vials behave better but for the price of a dramatic loss in shelf capacity. The RSD as well as the UF of the glass vials approaches the values of the COP vials. With an RSD of 7.30% for COP and 8.25% for glass vials as well as a UF_{COP} = 0.97 and UF_{Glass} = 0.98.

Although the final residual moisture is slightly higher for COP vials (0.84 ± 0.12%) compared to glass vials (0.57 ± 0.14%), the optical appearance as well as the cake structure is improved for COP vials. This provides the possibility, to apply more aggressive freeze-drying runs on products in COP vials, to equal the residual moisture level to products dried in glass vials instead of prolonging drying times, which would be a matter of time and cost. Even shorter drying times

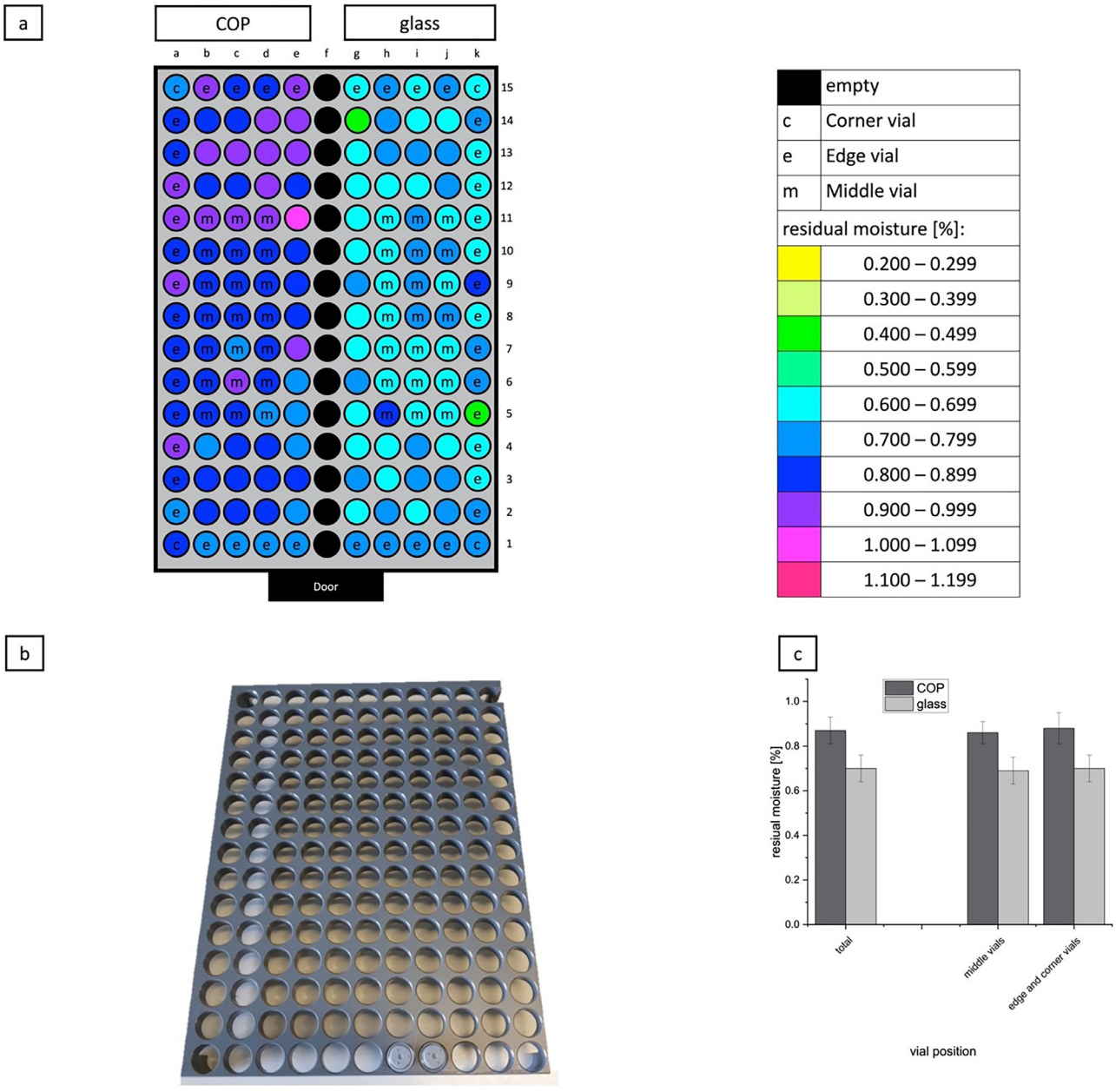

Figure 3. Summarized results of the placebo properties. Distribution of residual moisture in COP Vials and in glass vials (a). Picture of the used frame (b). The frame allows full shelf contact of the vial. Summarized residual moisture values (c).

resulting in elegant cakes might be feasible, when COP vials were used.

Another approach to achieve a better batch uniformity and improved cake appearance is controlled nucleation.[14] Here, also an increased batch homogeneity is achieved with slightly increased residual moisture compared to a standard lyophilization procedure. However, the most of this technique are not yet available for large scale production whereas COP containers might be more easily implemented as the filling lines as well as the COP vials themselves comply to ISO standards.

Conclusion

The concept to reach better product uniformity by using COP vials is proven. By the isolating thermal behavior of COP as material, the neighbouring-vial-effect was strongly reduced. A more homogenous heat transfer is provided in COP vial and can be seen in the r.m. measurements. Furthermore, although the products in COP vials remain at a higher r.m., no signs of collapse are present in the products. In contrast, shrinkage is visible in the products dried in glass vials but not in COP. Thus, it is possible that COP vials enable even more aggressive freeze-drying processes without structural collapse of the product than glass vials, also when transferred to protein containing formulations. With this, a higher r.m. level in COP vials can be easily overcome and even faster freeze-drying cycles with full preservation of batch homogeneity are possible. Also, a reduction of further excipients (e.g. mannitol), that are used as bulking agents to stabilize the cake structure might pe feasible. How to store freeze dried products in COP vials over long time and how to turn the drawback of higher gas permeability in COP vials positively has been discussed by Härdter et al. recently.[9] Furthermore, within the recent development of highly potent drugs (e.g. antibody-drug-conjugates or therapeutic viruses), a breakage resistant polymer container might be of advantage to protect the people during the development, production and shipment.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Carpenter JF, Chang BS, Garzon-Rodriguez W, Randolph TW. Rational design of stable lyophilized protein formulations: theory and practice. In: Carpenter JF, Manning MC, eds. *Rational Design of Stable Protein Formulations*. Vol 13. Pharmaceutical Biotechnology. US: Springer; 2002:109–133. https://doi.org/10.1007/978-1-4615-0557-0_5.
2. Randolph TW, Schiltz E, Sederstrom D, et al. Do not drop: mechanical shock in vials causes cavitation, protein aggregation, and particle formation. *J Pharm Sci*. 2015;104(2):602–611. https://doi.org/10.1002/jps.24259.
3. Wang W. Instability, stabilization, and formulation of liquid protein pharmaceuticals. *Int J Pharm*. 1999;185(2):129–188. https://doi.org/10.1016/S0378-5173(99)00152-0.
4. Butreddy A, Janga KY, Ajjarapu S, Sarabu S, Dudhipala N. Instability of therapeutic proteins — an overview of stresses, stabilization mechanisms and analytical techniques involved in lyophilized proteins. *Int J Biol Macromol*. 2021;167:309–325. https://doi.org/10.1016/j.ijbiomac.2020.11.188.
5. Rambhatla S, Pikal MJ. Heat and mass transfer scale-up issues during freeze-drying, I: atypical radiation and the edge vial effect. *AAPS PharmSciTech*. 2003;4(2):22–31. https://doi.org/10.1208/pt040214.
6. Ehlers S, Schroeder R, Friess W. Trouble with the neighbor during freeze-drying: rivalry about energy. *J Pharm Sci*. 2021;110(3):1219–1226. https://doi.org/10.1016/j.xphs.2020.10.024.
7. Hibler S, Wagner C, Gieseler H. Vial freeze-drying, part 1: new insights into heat transfer characteristics of tubing and molded vials. *J Pharm Sci*. 2012;101(3):1189–1201. https://doi.org/10.1002/jps.23004.
8. Vilivalam VD, De Grazio FL. Plastic packaging for parenteral drug delivery. In: Nema S, Ludwig JD, eds. *Pharmaceutical Dosage Forms - Parenteral Medications: Volume 1: Formulation and Packaging*. CRC Press; 2016. https://doi.org/10.3109/9781420086447.
9. Härdter N, Menzen T, Winter G. Minimizing oxidation of freeze-dried monoclonal antibodies in polymeric vials using a smart packaging approach. *Pharmaceutics*. 2021;13(10):1695. https://doi.org/10.3390/pharmaceutics13101695.
10. Sacha GA, Saffell-Clemmer W, Abram K, Akers MJ. Practical fundamentals of glass, rubber, and plastic sterile packaging systems. *Pharm Dev Technol*. 2010;15(1):6–34. https://doi.org/10.3109/10837450903511178.
11. Yoneda S, Torisu T, Uchiyama S. Development of syringes and vials for delivery of biologics: current challenges and innovative solutions. *Expert Opin Drug Deliv*. 2021;18(4):459–470. https://doi.org/10.1080/17425247.2021.1853699.
12. Daller S, Friess W, Schroeder R. Energy transfer in vials nested in a rack system during lyophilization. *Pharmaceutics*. 2020;12(1):61. https://doi.org/10.3390/pharmaceutics12010061.
13. Tang XC, Nail SL, Pikal MJ. Evaluation of manometric temperature measurement (MTM), a process analytical technology tool in freeze drying, part III: heat and mass transfer measurement. *AAPS PharmSciTech*. 2006;7(4):E105–E111. https://doi.org/10.1208/pt070497.
14. Geidobler R, Winter G. Controlled ice nucleation in the field of freeze-drying: fundamentals and technology review. *Eur J Pharm Biopharm*. 2013;85(2):214–222. https://doi.org/10.1016/j.ejpb.2013.04.014.