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Experimental and theoretical investigation of inhomogeneous lyophilization: The impact of the vials packing density and solid-phase resistance on the drying rate

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Abstract

Lyophilization is a proven method that is used primarily for drying thermolabile substances and chemically highly unstable drugs, such as proteins, vaccines, hormones, or even biopharmaceuticals. The freeze-drying process is slow and time-consuming and requires a rational design of conditions for individual drying steps. The freeze-drying cycle consists of three main steps: freezing step, primary and secondary drying.

Inhomogeneity is one of the problems of lyophilization that is still not fully understood. It's a phenomenon where peripheral vials placed on a shelf dry much faster than central vials. This observation can be influenced by several reasons, such as heat transfer from the walls of the chamber, different construction of the shelves, but also the effect of the packing density of the vials. In addition to the mentioned sources of inhomogeneous drying, the drying rate is effect by the resistance of the solid phase, which is formed during lyophilization in real solutions. In these solutions, not only heat transfer occurs, but the process is also affected by mass transfer, both of which cause differences in drying rate between the peripheral and central vials.

In this presentation we share experimental results of inhomogeneous lyophilization. Gravimetric measurements in all vials on a shelf were performed and evaluated using transient mathematical models of sublimation and primary drying. Distributions of heat transfer coefficients and pore resistances in vials are presented proving inhomogeneous distributions of heat transfer coefficient and its dependence on the packing density. On the other hand, the distribution of pore sizes is relatively narrow without a clear dependence on the location in lyophilizer.

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