Continuous manufacturing of lyophilized products: Why and how to make it happen

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Shortened title: Continuous lyophilization of pharmaceuticals

Abstract

This paper deals with the problem of continuous lyophilization of pharmaceutical products, focusing on those concepts that are of greatest interest and most likely to be successful once applied in industrial practice. Also, it discusses all those factors that slow down the transition from batch to continuous in the pharmaceutical industry, and what actions may accelerate this transformation.

Introduction

The pharmaceutical industry is concentrating most of its multi-billion dollar investments in the research of new drugs for life-threatening diseases [1]-[2]. Although these therapeutic solutions improve the quality of life of patients, leading to increasingly personalized medicine, their manufacturing process tends to be slow to innovate. Similarly, for established therapies, there are still wide margins of improvement for the manufacturing innovation.

In other sectors, the industry has responded to the growing demand for quality and access, developing substantially smaller, cleaner, more energy-efficient technologies, and then moving towards continuous production. The pharmaceutical industry has pursued this strategy, but this transformation is slow. For example, although continuous technologies have been commercially available for upstream for more than 25 years, e.g., perfusion cell culture, their integration with the downstream operations (e.g., chromatography, filtration, and lyophilization) is still under investigation. As a matter of fact, there are only 6 drug products that include continuous technologies in their manufacturing infrastructure, i.e., Daurismo by Pfizer, Orkambi and Symdeko by Vertex, Prezista and Tramacet by Johnson & Johnson, and Verzenio by Eli Lilly [3]. The main advantages of continuous manufacturing include:

- Eliminating scaling up from bench to manufacturing scale
- Operations do not depend on low-cost labor, but on advanced technology
- Drugs can be produced on demand, reducing stockpiles and risk of stock-outs
- Improvement in product quality and safety due to low residence times and no process breaks
- Viable route for personalized medicines and complex pharmaceuticals (e.g., cell and gene therapy, nucleotides, etc.)
- Ability to respond promptly to drug shortage

Historically, the pharmaceutical industry has always been conservative and reluctant to adopt new production technologies. This attitude stems from the belief that the introduction of new production technologies may cause new burdens for the company or delays in the approval process. That is a paradoxical situation. On the one hand, the pharmaceutical industry expects major regulatory challenges related to the implementation of continuous technologies while, on the other hand, regulators continue to encourage their development.

In recent year, the pharmaceutical community has admitted that continuous manufacturing might compete on both price and quality, and can better meet the requirements set by the regulatory authorities [4]-[5]. This situation set the stage for the entry of competition, paving the way to an unexpected change in direction. The transition from batch to continuous operations is, thus, the new challenge of

pharmaceutical manufacturing and, hence, of lyophilization as a downstream operation. The most powerful force driving this transition is the new global competition in throughput and quality. Despite the process has not changed in the last 80 years, the market for lyophilization equipment is expected to double in value to $4.8 billion within 2020. The introduction of new biologics and biosimilars will further increase the demand for lyophilization services and, hence, equipment.

Why we need continuous lyophilization

The interest in continuous lyophilization arises from the need to respond to the inefficiencies that characterize this process when it is conducted in batch mode. Despite batch lyophilization is a robust and established process, it has its weakness in long dead time, limited throughput, and poor control of the product quality and its uniformity.

Typically, a lyophilization cycle takes from a few days to a few weeks. However, the total cycle time can be much longer if we include the contribution given by the various ancillary operations that precede and follow the freeze-drying process. These operations include the loading and unloading of vials into the equipment, cleaning-in-place (CIP) and sterilization-in-place operations (SIP), filter integrity testing, venting/backfilling, and defrosting of the condenser. Overall, downtime has a severe impact on process efficiency and profitably.

Another disadvantage of batch lyophilization is its inability to deliver a uniform batch of vials, resulting in an unavoidable vial-to-vial and batch-to-batch variability of product quality. For example, the stochastic nature of nucleation results in vials that have different product morphology and, hence, different drying behavior [6]-[8]. The most modern control-freezing technologies can mitigate this phenomenon [9]-[13], but most of them have been developed and validated on bench-scale equipment and, thus, some concerns still remain on their scalability on industrial units [14]. Additionally, ill-defined thermal contact between the vials and the temperature-controlled shelves impacts on the heat transfer uniformity [15]-[16] which is further worsen by the edge-vial effect. Vials placed at the side of the batch receive more heat than those placed in the central part [17]-[18]. The non-uniformity in shelf temperature and chamber pressure further accentuates the batch heterogeneity during primary drying [19]-[20]. Overall, the inaccurate control of the heat transferred to the vial can result in a batch that does not meet specifications. For example, if the product exceeds its maximum allowable temperature, the entire batch of vials could be rejected because of aesthetic defects[21], loss of the therapeutic agent potency or unachieved residual moisture levels [23]-[24].

Lastly, a multitude of factors determine changes from batch to batch, and, unfortunately, precise control of process parameters can only mitigate unpredictable variations in material grade, changes in equipment performance and efficiency due to wear [25].

At the end of preclinical studies, the lyophilization cycle developed on small laboratory equipment has to be scaled up onto commercial scale units to respond the clinical and market demand. During this phase, the risk of failure is very high, and an extensive experimental campaign is usually required.

Examples of continuous lyophilization concepts

In the 1940s, several food companies took an interest in the potential offered by the continuous lyophilization of beverages such as tea and orange juice [26]. However, the first commercial scale lyophilizer, the Conrad system, was realized only in the 70s to respond to the growing demand for instant coffee [27]. Today, continuous lyophilization is a well-established practice in the food industry for many products such as beverages, meat and seafood, fruit and vegetables, and prepared meals. Nevertheless, none of these technologies respond to the many constraints imposed by the pharmaceutical industry, which thus still relies on batch-wise approaches.

In the last three decades, many concepts have been patented for the continuous lyophilization of pharmaceuticals in bulk, but they were not yet available in the market because of either their complexity or the difficulty of preserving the product sterility [28]-[29]. Most of these technologies are substantially based on three steps: the atomization of the pharmaceutical solution, freezing of the droplets, and

vacuum drying of frozen particles. Various drawbacks are impeding their application industry such as the challenge of filling the powder in adequately accurate doses, product handling interaction, and challenges in reducing the number of undesired particles [29]-[35].

Other researchers have thrown overboard the old idea of using spray freezing to realize a continuous flow of frozen material to be dried. Their attention shifted to systems that can manage a continuous flow of vials. In this direction, two promising technologies have a good chance of finding an application in the industrial field.

The former continuous concept combines spin or centrifugal freezing [37]-[39] and radiative drying [40]. The vials are longitudinally rotated at about 2500 rpm so as to spread the liquid solution on the vial side wall, which is, then, frozen by contact with a sterile cryogenic gas. The frozen vials are then transferred into a drying chamber operating at low pressure, where primary and secondary drying occurs. Here, each vial slowly rotates at about 5–12 rpm in front of its individual IR heat source.

The second concept was the result of a collaborative work between my research team at Politecnico di Torino and Prof. Trout's research team at Massachusetts Institute of Technology [35]. Figure 1 shows a schematic of the concept which is essentially based on a continuous flow of vials that enters and leaves the apparatus, passing through different specialized chambers.

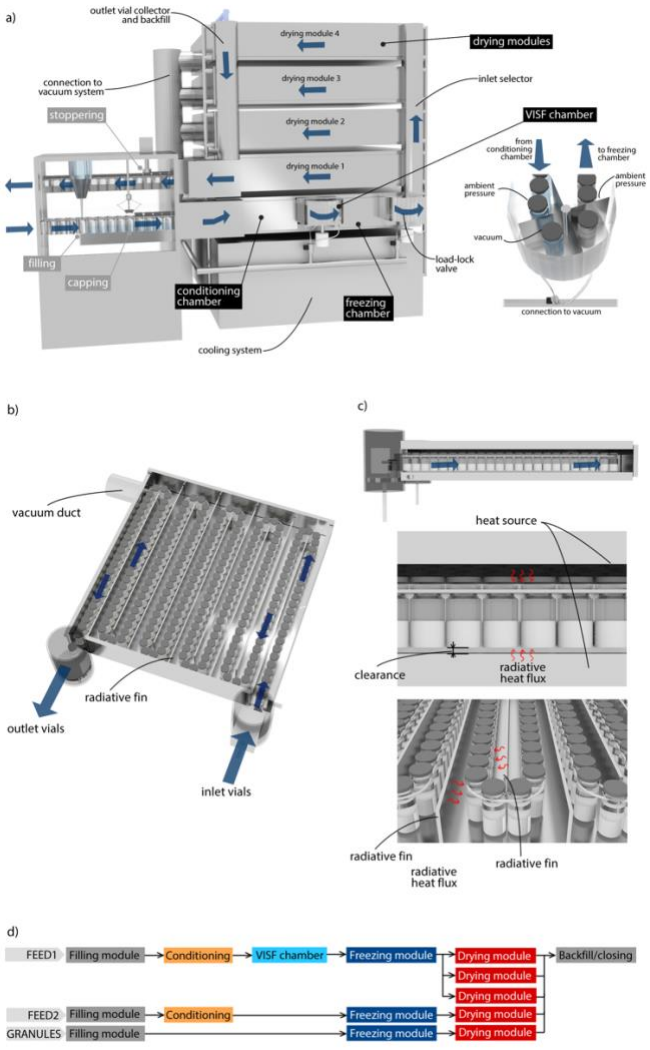

Figure 1. Schematic of (a) the continuous freeze-dryer and (b) a drying module. The front view of the drying module (c) and examples of potential configurations for the continuous lyophilizer (d) are also shown. The estimated chamber volume of the continuous lyophilizer (including both freezing and drying modules) is approximately 0.7 m^3. Reprinted with permission from [36]. *Source*: Copyright (2019) American Chemical Society.

After filling, the vials are suspended over a moving track and moved into the conditioning module. In this module, the vials are equilibrated at the desired temperature by forced convection with a cryogenic gas. The precooled vials are then transferred into a nucleation chamber, where ice nucleation is triggered via vacuum-induced surface freezing [10]. After nucleation, the vials are exposed to a cryogenic gas to complete the solvent solidification. The frozen vials are finally transferred to the drying module through a vacuum pass-through connector. The drying module is constituted of temperature-controlled walls that supply heat to the product via low-temperature radiation. By this concept, lyophilization is carried out continuously, without breaks between phases or manual intervention. Among the benefits of this approach are:

- Precise control of nucleation temperature;
- Vials go through the same path and, thus, undergo identical freezing and drying conditions;
- Heat is essentially transferred to the vials by radiation, thus small variations in the vial bottom have no significant effect on heat transfer efficiency;
- Drying can be carried out at the lowest chamber pressure compatible with the equipment capability, without influencing heat transfer and maximizing the sublimation rate;
- The primary drying time can be reduced by a factor of 2 to 4 times, and the total cycle time up to 10 times.

What the barriers are and how to overcome them

Despite manufacturing innovation is a key factor to ensure productivity growth, the development and implementation of continuous processes is expensive. Thus, these activities can actually be executed only by large companies, which have enough capital to invest and accept increased delays in investment returns. This implies that these initiatives must be promoted and supported at very high levels in companies, including the board of directors.

The transition from a well-known and consolidated technology, including regulatory processes, to a completely new production platform is further hindered by the lack of qualified personnel. Furthermore, production staff often obstruct the implementation of new technologies because their introduction is often imposed by senior managers and involves a considerable effort to adapt to new procedures and acquire new skills.

How to make it happen

Continuous lyophilization can contribute to reduce costs and increase flexibility of pharmaceutical manufacturing facilities. Compared to batch, continuous technologies are characterized by smaller equipment size, lower capital and operating cost. It is, therefore, indisputable that the benefits of continuous manufacturing are immense, but major investments are necessary.

Given the need for companies to manage the risk of investment in new technologies, we need tax and regulatory incentives. The former, e.g., promoted the growth of pharmaceutical manufacturing hubs in Ireland and Singapore.

Public funding is, therefore, essential to support competitive R&D programs and promote collaboration between national research and innovation clusters in the manufacturing sector. Further investments in these infrastructures are needed and can promote initiatives to enhance the exchange of knowledge and technology transfer.

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