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Review article

# Achieving continuous manufacturing in lyophilization: Technologies and approaches

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ABSTRACT

This paper provides an organic overview of the most interesting continuous freeze-drying concepts that have been proposed over the years. Attention has mainly been focused on the field of pharmaceuticals, but some background has also been given on the food industry. This work aims at providing a solid starting point for future research on continuous manufacturing for the freeze-drying of pharmaceuticals.

## 1. Introduction

Continuous pharmaceutical manufacturing is considered an emerging technology that will radically change the pharmaceutical industry. The adoption of continuous manufacturing could offer flexibility to the process, higher product quality and economic advantages that pharma companies need in order to face their future challenges: new markets and new players on the market, lower revenues, higher standards of quality, increasing complexity and a declining R&D productivity. Freeze-drying in the pharma industry, as a downstream operation in the pharmaceutical production chain, also needs to follow these tendencies. It is not easy to exactly quantify how many of the lyophilized products would require the improvement in process efficiency ensured by continuous manufacturing. However, the augmented efficiency is not the only, or main, reason that would make the shift to continuous manufacturing advantageous. For instance, all lyophilized products would certainly benefit from the improved quality control and greater flexibility guaranteed by a continuous process.

It is our opinion that an organic overview of the continuous freeze drying concepts proposed so far, which have never been categorized before, would be beneficial for further developments in this field of study. Thus, the present work is aimed at covering this gap, and, in order to do so, lyophilization patents and papers published over the last seventy years have been analysed, in order to provide an as comprehensive as possible review of the work carried out so far and of the problems that have not yet been solved. To accomplish this goal, a classification criterion was chosen to obtain a clearer description of the progress achieved over the years. We decided to distinguish between two different categories of freeze-dryers: 1) freeze-dryers that are fed with bulk material, supplied either as frozen granules or in liquid form. In this case, the dosage of the final product into a suitable vessel is performed at the end of the drying process, and 2) freeze-dryers that work on and directly produce unit-doses. In the latter case, the dosage is carried out as the first step, and the product is dried after being introduced into a vial or another suitable container.

Category 2 is the most suitable for pharmaceutical products, as it allows an easier control of sterility (the product is never in contact with the mechanical parts of the dryer, but only with the walls of the final container) as well as an accurate dosage of the APIs. However, category 2 equipment must be designed to take into account the huge variety of shapes and dimensions of containers commonly used in freeze-drying, which can be a challenge. This problem would not arise in the case of category 1, where a simple fluidized bed, or a vibrating system, may be used to handle the product through the different sections of the dryer. Because of this, most of the early concepts of continuous freeze-dryers proposed over the years fall into this first category.

Therefore, the following sections deal with the aforementioned two categories of continuous freeze-dryers, and each class is analysed from a chronological point of view.

### 1.1. Current trends in the pharmaceutical industry

The pharmaceutical industry is facing a period of significant change pertaining to: new drugs and dosage forms, the expiry of some high-profit drug patents, new competitors and markets, and the setting of more stringent standards by regulatory authorities. To respond to this

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wave of competing challenges and, at the same time, to a period of stagnant growth, many pharmaceutical companies are consolidating their position by demonstrating the clinical and economic value of their products, adopting new technologies, elevating their quality standards and, finally, rethinking their production and distribution structures [1].

From the processing point of view, the main challenge that has to be faced is the competition for cost-effective drugs and the increasing regulatory authority scrutiny [2]. In this perspective, the strategy adopted by some big pharma companies is that of the so-called "Toyota model", which consists in moving from a traditional production model to a highly responsive, lean, manufacturing one (Fig. 1). The next step would naturally be to move from batch to continuous production. Some pharma companies are still moving in this direction, in part thanks to the support of regulatory authorities, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

### 1.2. Batch vs. continuous manufacturing

The pharmaceutical industry generally adopts batch manufacturing, which consists of a series of separate unit operations.

- A batch process is constituted by a predefined sequence of discrete tasks, in which raw products are charged into the system at the beginning and discharged after a pre-set time.
- In continuous manufacturing, processes are integrated, on the basis of a systems approach that makes use of model-based control and flow [4]. The number of partitions is minimized, quality control is performed inline, and the request for personnel is reduced. Moreover, processes can be operated 24 h/day, 7 days/week, with infrequent planned maintenance shutdowns. No transient or dead times are present, and the distinction between upstream and downstream is overcome [4].

The main advantages of continuous processes over batch ones are [5]:

- Operation flexibility
- Shortening the time to react to changes in market demand
- Reduced scale-up issues, or no scale-up at all
- Real-time quality assurance
- Reductions in footprint, investment and operative costs

In spite of the superior efficiency of continuous processes, most drugs are at present almost exclusively manufactured using the batch technology. For example, it has recently been estimated that only 5% of pharmaceutical processes are carried out continuously [6]. This means that the current manufacturing practice consists of a series of segmented process steps, often performed in different facilities around the world. As a result, batch manufacturing introduces such a significant lag-time between technical operations that the cycle time from the start of manufacturing to the delivery to patients can be extremely long. This practice limits the ability of a manufacturing process to react quickly to changes in demand of a newly launched product or when a large volume of medicine is needed in a relatively short period of time.

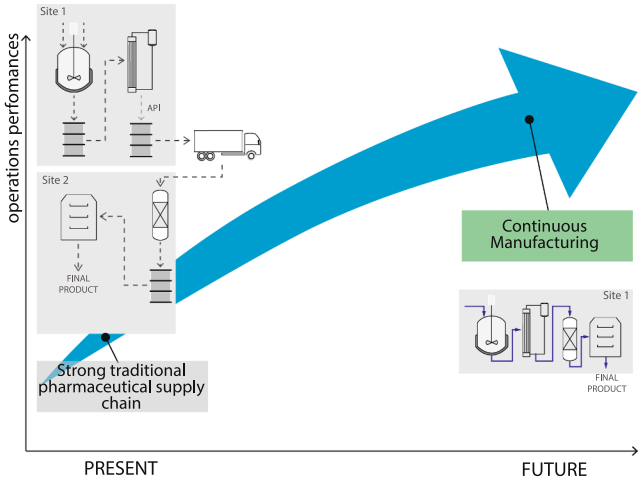


**Fig. 1.** Present and current trends in the pharmaceutical industry [3].

Continuous manufacturing would not only result in increased productivity, but would also be more reliable and safer, eliminating breaks between steps and reducing opportunities for human errors during the typical stops and starts of batch processes. Moreover, a more efficient production of quality products can reduce manufacturing costs, possibly resulting in lower drug prices for consumers, and would allow manufacturers to respond more quickly to changes in demand. Finally, the equipment footprint would be smaller, thus decreasing the costs and introducing more flexibility [7,8].

### 1.3. Early and ongoing implementation of continuous manufacturing in the pharmaceutical industry

The pharmaceutical industry has already made some progress in implementing stepwise continuous processes, in both the synthesis of Active Pharmaceutical Ingredients (APIs) and in the production of the final dosage forms [9]. For instance, continuous equipment has been proposed for granulation [10–12], crystallization [13] and for reactors [14–18]. Some efforts have also been made recently to integrate all these separate steps into a continuous end-to-end process. In particular, a team of researchers at the Novartis-MIT Center for Continuous Manufacturing have demonstrated the concept of Integrated Continuous Manufacturing (ICM) for pharmaceuticals by developing a process that goes from synthesis to pills without pauses [19]. The system consists in developing well-understood, smaller-scale process technologies that can be integrated in an end-to-end manufacturing process for pharmaceuticals. In this way, raw materials can be transformed into finished tablets without interruption, thus enhancing the performance of the entire process. The same team has also developed a continuous process for the development of Aliskiren and the production of coated tablets [20].

In Europe, the Centre for Innovative Manufacturing for Continuous Manufacturing and Crystallisation (CMAC), at the University of Strathclyde, is working, in collaboration with industries, on developing new continuous processes, while GlaxoSmithKline is building a continuous manufacturing plant in Singapore for antibiotic production [21].

The benefits of continuous manufacturing have been investigated extensively [22–26], and interest in this field is demonstrated by the survey performed recently by the ACS GCI Pharmaceutical Roundtable [27]. Currently, the Roundtable consists of 15 corporations: Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Codexis, DSM, Dr. Reddys, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Novartis, Pfizer, Roche, and Sanofi. The survey focused on the status of the implementation of continuous processing and was aimed at elucidating the stakeholders' opinions, possible fields of application and potential hurdles. According to the survey, there is clearly significant interest in continuous processing among large pharmaceutical companies. In fact, all of the aforementioned companies were found to have a dedicated group within their Research and Development departments working on continuous processes, even though the size of investment and degree of implementation varied significantly. The companies that answered the survey generally agreed that increased throughput, easier scale-up, improved safety and control, and reduced cost and waste were certainly among the benefits of implementing continuous processing [27]. On the other

hand, the main hurdle appears to be concerns about the important investments that are needed in continuous manufacturing, especially considering that sufficient productivity of conventional batch processes is available. Other problems related to the implementation of the new technology are a lack of personnel with adequate knowhow, as well as technical difficulties with the presently available systems.

However, some commercial drug processes have already been made continuous, such as the production of the cystic fibrosis Orkambi tablets by Vertex [28] or the manufacturing of Prezista, the drug developed by the Janssen Supply Chain for the treatment of HIV-1 [29]. Chinoin is also at present commercializing a drug, i.e., Severin, by means of continuous equipment [30,31].

### 1.4. Regulatory perspectives

The progress towards continuous manufacturing has been facilitated, in recent years, by regulatory agencies [8,29].

For instance, in 2002, the FDA launched an initiative called *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach* [32], which has the aim of promoting new technology advances in the pharmaceutical industry.

The next step was the release of an additional guidance on manufacturing, entitled *PAT-A Framework for Innovative Pharmaceutical Development Manufacturing and Quality Assurance* in 2004 [33]. This guidance describes a regulatory framework in which industry and government can work together to increase the level of innovative pharmaceutical manufacturing technologies and, in this framework, the development of continuous processing is described as beneficial for both the quality of the product and the efficiency of the process.

On December 2015, FDA released a draft guidance to industry [34]. This document discusses a new FDA programme that allows pharmaceutical companies to submit proposals about the use of innovative technology to the Emerging Technology Team (ETT), a group that is part of the Center for Drug Evaluation and Research (CDER). ETT will thus work directly with pharmaceutical companies to evaluate proposals, thus facilitating the review process for companies interested in implementing new manufacturing technologies. Recently, the FDA published draft Guidelines for continuous manufacturing [35].

Moreover, in 2014 Janet Woodcock, Head of CDER at the FDA, expressed the desire to set up a constructive dialogue about continuous pharmaceutical manufacturing with industries and academics [36]. Thus, in 2014, MIT and the Continuous Manufacturing and Crystallisation Consortium (CMAC) organized a symposium to accomplish this goal. The 2014 edition was a great success and saw the active participation of the most important pharmaceutical companies, as well as contributions from various universities. A second edition was organized for September 2016, with focus on case studies pertaining to the implementation of continuous manufacturing.

During these symposiums, the discussions covered all the aspects involved in continuous manufacturing, including regulatory and quality considerations [8], recent advances in single unit operations [37,38], as well as case studies of end-to-end processes [39,40].

FDA is not the only agency to have promoted the shift towards continuous manufacturing. Among others, in 2016, the US government's National Science and Technology Council (NSTC) defined continuous manufacturing of pharmaceuticals as a priority objective of US industry [41]. Moreover, the European Medicines Agency (EMA) has also endorsed innovation in manufacturing, especially pertaining to continuous approaches [42]. Finally, in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has been encouraging industry to introduce innovative continuous manufacturing technologies [43].

## 2. Freeze-drying of pharmaceuticals and biopharmaceuticals

In spite of the increasing attention given to continuous manufacturing, there are still some pharmaceutical processes whose progress in this field is unsatisfactory, and freeze drying is certainly among them. This technique consists in a low-temperature drying process, which is particularly suitable for heat sensitive products, and is thus used widely for the production of pharmaceuticals.

Freeze-drying allows a significant increase in the stability of pharmaceuticals and biopharmaceuticals, and, thanks to the mild conditions employed, can effectively preserve the activity of APIs.

However, pharmaceutical freeze-drying is at present an expensive and time-consuming operation, and this is worsened by the fact that it is a batch process. Moreover, in batch freeze-dryers, the heat transfer provided to the product is uneven, and this leads to vial-to vial inhomogeneity, and, thus, to the impossibility of guaranteeing the same quality in each unit dose. Other drawback of the presently available system are the complicated handling of vials during loading and unloading, which increases the risk of contamination, the lack of versatility and the difficult scale-up. Thus, the shift from batch to continuous would allow a great saving of time, an increased productivity, a better quality and homogeneity of the final product, and improved flexibility to be achieved [44].

### 2.1. Relevance of freeze-drying in the pharmaceutical industry

The modern history of freeze-drying started in 1890, when freeze-drying was successfully applied by the histologist Richard Altman to preserve tissues [45]. Many other successful attempts were then made by Benedict and Manning in 1905 and by Shackell in 1909, until, in the 1920s, freeze-drying became a common and established drying method of tissues and biological materials [46]. In 1933, the aseptic freeze-drying of blood serum was carried out at the University of Pennsylvania by S. Mudd and W. Flosdorf [47]. The first application of freeze-drying on a large-scale appeared in 1945 for the production of penicillin. From that point on, the freeze-drying process has been performed using a single chamber in which freezing and drying take place, a mechanical refrigeration system which supplies energy to the product and feeds the condenser, and a vacuum pump, which is used to evacuate uncondensable gases [48].

From the 1950s until the present day, an increasing number of products have been freeze-dried, i.e., antibiotics, vaccines, oncolytics, corticosteroids, as well as surgical and diagnostic products.

### 2.2. Drawbacks of batch freeze-drying

The freeze-drying of pharmaceutical products is carried out using large equipment placed in sterile rooms. The process consists of three main steps:

1. Freezing of a liquid solution until complete solidification of the product has occurred.
2. Primary drying, which consists in removing ice by sublimation. The process variables, i.e., the chamber pressure, shelf temperature, and duration, are adjusted to avoid the collapse or the melting back of the product.
3. Secondary drying, which consists in removing the residual water adsorbed in the solid cake. This step is performed in a vacuum condition and with an increasing shelf temperature to trigger water desorption.

Batch freeze-dryers can be easily designed and are currently available in most manufacturing sites. They also allow a good sterility control, and make it possible to achieve an accurate dosage of the APIs. Significant investments would be required for their substitution with a continuous line, and a specific training would be needed to operate and maintain the new equipment. These are the main advantages of batch freeze dryers. However, several drawbacks of the batch technology exist, and will be listed in the following.

*2.2.1. Processing and downtime*

A typical freeze-drying cycle ranges from few hours to more than an entire week, depending on many variables, e.g., product formulation, filling volume and vessel type. The downtime between two consecutive cycles is usually long because some ancillary operations are required:

1. vial filling, vial loading, vial unloading, vial stoppering
2. venting/backfilling
3. leak test
4. cleaning-in-place (CIP)
5. sterilization-in-place (SIP)
6. condenser defrosting
7. filter integrity test

Vial filling, loading, and unloading in the drying chamber and vial stoppering is carried out in sterile conditions by mean of automatic systems that minimize human intervention. These systems are usually able to process 500 vials per minute, which means that these operations take from 6 to 10 h for industrial-scale batches. Moreover, condenser defrosting, CIP, SIP, a leak test and a water intrusion test take from 7 to 13 h [49,50].

*2.2.2. Freezing process and its control*

Freezing is a fundamental step in lyophilization and an important cause of vial-to-vial and batch-to-batch non-uniformity. During this process, ice nucleation occurs stochastically in a supercooled solution, and crystals then start to grow. Finally, a multiphase system is formed with several domains, i.e., crystals of pure ice and other solid phases constituted by the drug, the excipients and the bound water. Therefore, the microscopic structure of the product, crystallinity and polymorphism, and the stability of the APIs are influenced to a great extent by the thermal history of the samples during freezing [51–53]. Unfortunately, each sample has a different thermal history, since nucleation is a stochastic event and eventually shows different product characteristics. Vacuum induced surface freezing [52,54–57], ice-fog [58–62] and high pressure/depressurization [63–65] are all used in freeze-drying to control nucleation, but many issues remain when these processes are applied in an industrial freeze-dryer [66].

*2.2.3. Primary and secondary drying*

During drying, the main cause of non-uniformity is the differences in the heat transfer. These differences may be attributed to variations in:

1. Vial geometry/shelf flatness
2. Position of vials on the shelf
3. Shelf surface temperature
4. Chamber pressure

Heat is supplied by contact between the vial and the shelf, gas conduction in the small gap between the shelf and vial, and by radiation from shelves and the surroundings. As each vial may be slightly different from the others, the heat supplied to the product changes. A second important effect is due to the position of the vials on the shelf; vials in the proximity of walls can receive up to 50% more heat than those in the centre. The extensive literature on the so-called ”edge-vial effects” shows how important their impact is in performing safe and reliable cycles. The non-uniformity of the temperature across the shelves and the pressure gradients in the apparatus represent a further source of non-uniformity in the heat supplied to the products [67–70].

*2.2.4. Batch-to-batch variability*

Batch-to-batch variability is a typical problem of every batch process. Variations in product quality and in the characteristics from batch to batch are usually unpredictable, and even a perfect control of the process is not sufficient to avoid them. Any changes or deviation, such as changes in suppliers, different equipment or human errors, can seriously affect product quality and safety. A Quality by Design approach can partially mitigate this variability, thus assuring a quality target [32,71–73].

*2.2.5. Scale-up*

Scale-ups play a critical role in achieving reliable and efficient cycles. In fact, when moving from the laboratory to pilot equipment, and eventually to an industrial freeze-dryer, many variables have to be taken into account. The typical cycle scale-up and transfer issues are [74,75]:

1. no GMP conditions of the pilot equipment vs GMP/particulate-free condition of the industrial equipment
2. long loading times of industrial batches
3. Differences in the heat transfers
4. Variations in the cake resistance
5. Variations in the shelf temperature
6. Spatial variations in the chamber pressure
7. Process control

*2.3. Emerging technology in freeze-drying process*

Continuous lyophilization has been carried out in the food industry since the 1960s, but in the pharmaceutical-freeze-drying world, research has mainly been focused on process monitoring and control [76–80] as well as on optimization of the product quality and uniformity [81–86]. Moreover, even though it is true that some concepts of continuous freeze-drying have also been proposed for pharmaceutical products, none of them has yet been applied successfully in the industry. The delay in the pharmaceutical industry, with respect to food production, is due to the much stricter requirements of sterility, product quality, and accurate dosage in the case of drugs. Since, at present, continuous freeze dryers do not allow a perfect control of these parameters, they have still not been considered suitable for large-scale industrial production.

## 3. Continuous freeze-drying of bulk material

This is the most common category of continuous freeze-dryers proposed over the years, mainly because of the relatively simple design of continuous systems working with bulk material, supplied either as frozen particles or in liquid form.

*3.1. Freeze-dryers working on granules: advances in the food industry*

Several freeze-dryers that work on granules have been proposed for the food industry, starting from the middle of the 20th century. A continuous freeze dryer pilot plant for drying orange juice was developed as early as 1945 [87,88]. Since then, the technology has improved rapidly, and continuous freeze-dryers have been used in the food industry since the 1960s.

For instance, Oetjen developed a continuous process for the production of powdered milk. According to this concept, freeze-dryer trays are filled with frozen products, in granular form, and driven through a drying tunnel while hanging from a monorail. The heat provided by heating plates, combined with vacuum conditions, promotes the removal of water from the product. The process is accomplished in successive steps and vacuum locks are used to connect the different sections of the apparatus [89].

*3.1.1. The Conrad system: a semicontinuous approach*

Another possible solution, in the food industry, is represented by the Conrad freeze-dryer, developed by Atlas [90]. The Conrad process is automatic, thus requiring minimal human intervention. Trays with frozen products are loaded into the dryer, through an airlock system,

and moved to an inlet elevator. When the elevator has been filled with trays, they are moved into the drying zones. A second elevator is used at the dryer exit to unload the trays, again through an airlock. Vapor removed by sublimation is collected on the internal condensers, which are equipped with a continuous de-icing system that enables automatic de-icing under vacuum. The products that can be freeze dried in the Conrad system fall into three categories, namely, liquids, individually quick frozen (IQF) products and combined products. Liquid products, such as coffee, tea and juices, are first frozen and then granulated and sieved to produce granules of optimum size. The granules are then loaded onto the Conrad trays. IQF products, including fruit, berries, seafood, meat and vegetables, are placed directly onto the Conrad trays. Combined products, e.g. baby foods or soup blocks, are instead generally loaded into special plastic moulds and frozen in a tray freezer before being transported to the Conrad.

#### 3.1.2. Development of a fully continuous line

The Conrad technology works but it is still a semi-continuous process. However, in the mid-1970s, a fully continuous line was introduced for the production of instant coffee. The granulated product is loaded continuously onto a 20–30 m long vibrating tray placed inside a drying chamber. The product moves along the tray fluidized by its own water vapor, while heating devices provide the energy necessary for sublimation. Unavoidably, attrition between product and tray generates a dust that is made up of small particles, and a screen is used to prevent these particles from reaching the condenser and the pumps [89].

At present, continuous freeze-drying tunnels are manufactured for the food industry by, among others, GEA, ALD, BUCHER, DEVEX, SSP, SPX and CUDDON.

### 3.2. An overview of registered patents

Several patents regarding continuous freeze-dryers that work on granules, or on bulk material in general, have been registered over the years.

#### 3.2.1. Frozen granules as raw material

Fuentevilla, for example, proposed a system in 1966 [91], in which the material to be freeze-dried is supplied preferably in powder or granular form and in a frozen state. This frozen material is placed in a refrigerated chamber, located above a feeding hopper. The purpose of the refrigerated chamber is to keep the material that has to be dried in a frozen state. Before loading the material into the dryer, the housing containing the refrigerated chamber is evacuated to a pressure equal to that of the vacuum chamber. At this point, the material that has to be dried is dropped into the feeding hopper, which, in turn, discharges the material onto vibrating trays, and it is then divided among a plurality of channels. The trays can also be heated, for example, through electrical current, by circulating hot water, or by radiation. Microwave generators may be used, at the end of the vibrating trays, to speed up the removal of residual moisture, while a discharge hopper drops the material into a previously evacuated vacuum lock. A moisture sensing device, connected to a control device, is used to control the vibrator and/or heating means in order to achieve optimum drying. Fuentevilla claimed that this apparatus could be used to freeze dry foodstuff, biologicals and pharmaceuticals.

#### 3.2.2. Processing of liquid substances

Although the apparatus by Fuentevilla works on already frozen particles, the equipment described by Vigano in 1966 [92] was designed to be fed with liquid substances. The liquid that has to be lyophilized is first introduced into a vacuum-tight container, where a preliminary degasification is performed, with a consequent cooling to about $+4$ °C. A controlled amount of this material flows through a valve and is spread, as a thin layer, over the inner surface of a cylindrical, continuously evacuated container. Owing to the low pressure in this cylinder, the liquid film evaporates and is frozen instantaneously. After completion of this step, sublimation, promoted by the pressure gradient and the heat provided by a heating element, can begin. The solid residue adhering to the wall is then scraped off using a brush and it falls, by gravity, in the form of a powder towards cyclone separators, and, eventually, towards a collecting tank. Centrifugal vacuum pumps, connected to the cyclone separators, are used to lower the pressure to a sufficient level to induce sublimation. The author claimed that this new apparatus allowed a remarkably higher production rate to be achieved than the previous ones.

#### 3.2.3. Progress towards increased productivity

Again in 1966, Togashi and Mercer [93] proposed another concept for foodstuff. The authors lamented that no rapid freeze-drying process was then available, because supplying the heat necessary to convert ice to vapor at high rates could overheat the outer portion of products. Another problem was related to the handling of large volumes of vapor. In this regard, previous concepts suggested maximizing the vapor flow velocity during its journey from the sublimation zone to the pumps that remove it from the system. However, the authors claimed that the overall rate of production could be increased, without any deterioration of the quality, just by limiting the vapor velocity to only a small fraction of the theoretical maximum velocity. They in particular found that the vapor velocity should range between 3% and 20% of the arithmetical average molecular velocity of the vapor under the conditions that existed along the flow path. Moreover, the authors proposed a new freeze-drying apparatus, in which rapid drying could be accomplished. The raw material is introduced into the apparatus in a liquid state. After pasteurization, the product is frozen and then comminuted or ground to particles of a uniform size. Solid products can also be fed to the apparatus. In this case, such products would first be frozen and then shredded or cut. The frozen particles are then introduced, through an air lock, into trays located in the drying chamber. These trays are bound on each side by cryoplates, which are used to maintain a low pressure. The trays are vibrated, and a suitable means is provided to remove the ice that forms on the cryoplates. The heat required for sublimation is preferably supplied in the form of radiant heat.

#### 3.2.4. Material handling I: minimising mechanical damage

Another piece of apparatus designed for foodstuff was proposed by Rockwell et al. [94] in 1967. The authors claimed that it was suitable for both solid foodstuff, such as peas, berries, grapes, etc., and for liquid materials, such as juices, extracts, purees and concentrates. However, these materials had to be supplied in a frozen state and in the form of globules, pellets or dice. During operation, the material is fed, through a vacuum lock valve, into a chute, which then discharges the material into a feed cylinder. A feeding screw then provides the advancing motion necessary to transfer the frozen particles to the drying tubes. These tubes extend through a rotatable drum, which is mounted inside a vacuum vessel. The rotation imparted to the drum is either continuous or, preferably, intermittent, in order to minimize lodgement of particles in the drying system. The dryer is sloped towards the discharge end to facilitate progression of the material, while the heat required for sublimation is provided by means of steam, which is circulated inside the drum. An important feature of the drying tubes is that they are polygonal in the cross section, thus causing the particles to undergo a positive tumbling action and guaranteeing a uniform and fast dehydration. According to the authors, the advancing motion is achieved with minimum mechanical damage, and should be designed so as to keep the drying tubes at about 1/3 to 2/3 full of material. A discharge screw at the exit from the dryer is used to transport the dried particles towards a chute and, eventually, towards a vacuum lock valve.

#### 3.2.5. Material handling II: the dancing motion of frozen particles

An evolution of the concept introduced by Togashi and Mercer was proposed in a patent, dated 1972, by Mercer et al. [95] The authors

claimed that the new apparatus was suitable for liquid food and biological substances. The material, in a liquid state, is frozen as a thin sheet on a continuously moving belt and is then broken into pieces of a suitable size for freeze drying. This is accomplished by a series of comminuting means and screening devices. Frozen particles are then moved on a vibrating conveyor through an evacuated chamber, where condensers and radiant energy sources cooperate in the sublimation of ice. The introduction and removal of a product from the drying chamber is performed by means of vapor locks and suitable hoppers. The vibratory conveyor inside the evacuated chamber is made up of a series of vertically spaced vibrating decks, bound on each side by a series of condensers. The frozen particles move with a bouncing or dancing motion, and are periodically rotated and turned over by the vibrating action of the conveyor, and also by steps provided at spaced intervals on the upper conveyor surface. The condenser plates are periodically de-iced by a suitable device, so that the ice falls to the bottom of the drying chamber, where it is collected on a belt conveyor for removal from the system. The removed ice is first reduced in size, by means of a breaker, and then discharged through vapor locks. According to the authors, this system is able to accomplish freeze-drying in short times, that is, from 40 to 110 min.

### 3.2.6. Material handling III: avoiding product thawing

A similar idea was presented in a patent registered in 1971 by Oetjen et al. [96]. The authors proposed comminuting a frozen product inside a vacuum chamber. They claimed that this could solve the problem of the thawing of part of the product, which generally occurrs when comminution and screening of particles are carried out outside the drying chamber. The material, after being frozen outside the dryer into large chunks, is broken inside the chamber and comminuted into particles of appropriate size ready for drying. An automatic hopper, connected to a vacuum pump and to the drying chamber by means of a vacuum lock, feeds the material to a series of vibrating screen conveyors. Each screen conveyor has openings that are equal in size to the optimum size of particles for drying. Particles which are already at the desired optimum size for freeze-drying pass through these openings and go directly to the drying beds. Large chunks are instead driven towards comminution devices for a further reduction in size. After proper comminution, the particles are moved towards a series of vibrating drying beds, which are heated by means of a heating fluid, such as hot steam. Finally, a discharge hopper is attached to the end of the drying chamber and the dried product is removed through a vacuum lock. A scheme of the Oetjen freeze-dryer is shown in Fig. 2.

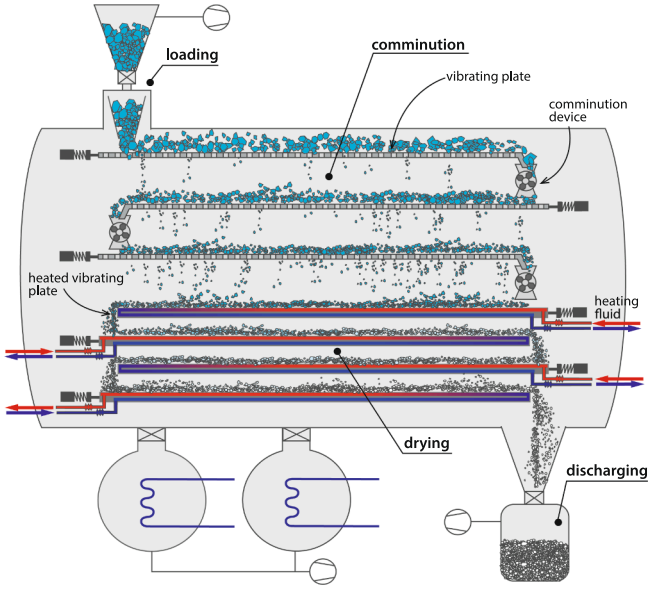


**Fig. 2.** Scheme of a continuous freeze-dryer concept, as proposed by Oetjen et al. [96].

### 3.2.7. Material handling IV: avoiding the release of volatiles and loose particles

Two patents were then proposed by Smith in 1971 and 1973, respectively [97,98]. According to the author, a typical problem of contemporary continuous freeze dryers was that the product could not be introduced into the vacuum vessel in liquid form, because volatiles in the product would flash into vapor as a result of the low pressures that were employed, possibly resulting in a decrease in quality. Therefore, the product was generally converted into a frozen powder and then introduced into the vacuum vessel. The problem with this, however, was that loose particles may bounce or fly off the conveyor, resulting in a deleterious build-up of powdered product within the vessel. Moreover, the layer of product had to be relatively thick for the apparatus to handle an acceptable volume of material. This made it difficult for radiant energy to penetrate the centre of the product layer, which also had low thermal conductivity. Thus, the two patents he issued in the 1970s were aimed at solving these problems. In the earlier one [97], the material is frozen, preferably in the form of a finely divided powder. The frozen powder is then moved from the freezing apparatus onto a conveyor. A pressure roll and a back-up roll are used to exert pressure on the frozen powder, thus bonding the particles to each other and to the upper surface of the conveyor. This eliminates the problem of product particles bouncing or flying off the conveyor. Moreover, fusion of the particles increases the conductivity of the product layer and decreases the thickness of the product layer, thus increasing the rate at which the product can be dried. The product is then heated by radiators at a low pressure in order to remove moisture by sublimation. The evolved volatiles are condensed and removed by means of a suitable sorbent, such as cold lithium chloride brine. After leaving the radiator, the heat transfer fluid is employed to heat and concentrate the sorbent and/or to generate steam to operate an absorption-type refrigeration system in order to cool the sorbent. This device led to a remarkable increase in efficiency, but a further improvement of this concept was presented two years later [98]. In the second patent, Smith proposed introducing the liquid or semiliquid product into a freezing compartment in an evacuated vacuum vessel and allowing it to form into a layer on an endless belt or other conveyor. The conveyor is then cooled or chilled to freeze the product on it. The pressure in the freezing compartment is maintained above the vapor pressure of the product so that volatiles will not evolve from it as it is spread over the conveyor. The frozen product is then brought to a drying compartment, where the pressure is set to a much lower level, and moisture is sublimed by radiant heat. Thus, the product in this apparatus is not granulated, but is instead processed as a compact bulk material.

### 3.2.8. Freeze-dryer based on a screw conveyor

In May 1973, Gottfried [99] proposed another idea, which he considered suitable for food and biological materials. Raw material is first frozen, while it travels along an elongated chamber, driven by a screw conveyor. The travel path is surrounded by cooling coils and the screw conveyor terminates in a crushing area, where the frozen product is crushed and triturated. The frozen particles are then transferred to a lyophilization zone, where they are kept in constant movement by an agitating device, e.g., screw conveyors. Moisture is removed from the drying zone by means of a vacuum pump and this zone is surrounded by a reversible refrigerator coils. The treated material is then transferred to one of three chambers of the finishing zone, which are also cooled or heated by the reversible refrigerated coils. The finishing zone has three different chambers, because the processing time in these chambers is about three times that required for the processing in the lyophilization zone. When the material in the finishing chambers is completely dried, the temperature tends to rise, and when the material reaches ambient temperature, a signal lights up. The product is then transferred to

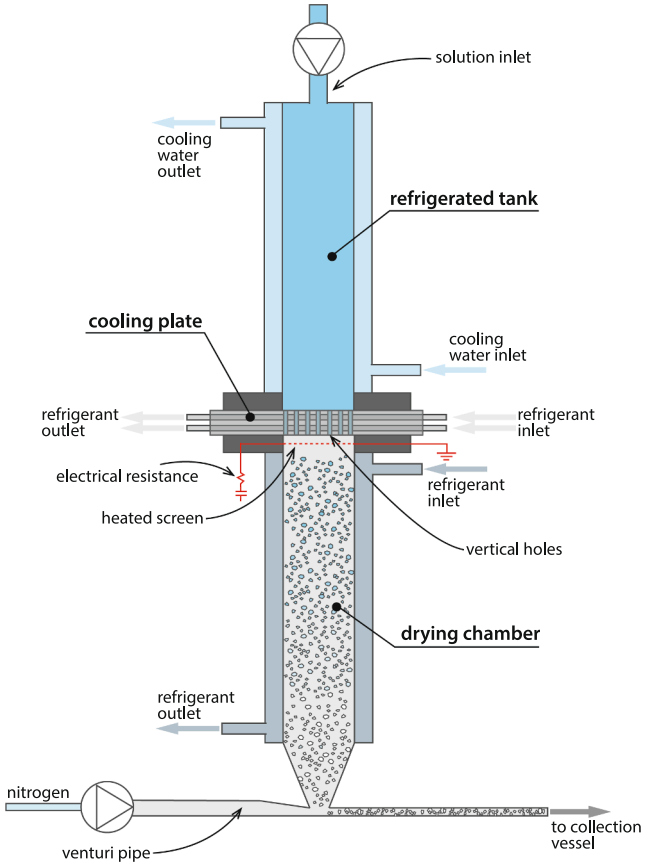


**Fig. 3.** Scheme of the continuous freeze-dryer concept proposed by Arsem [100].

appropriate containers.

### 3.2.9. Pressure drop provided by the freezing of supplied material

Although the previously mentioned concepts, despite their differences, all have similar features, a completely new idea was presented by Arsem in a patent dated 1986 [100]. In his apparatus, a material slurry is delivered, under pressure, to the inside of a refrigerated tank, where it is freeze-dried. This slurry is of an aqueous nature, and could be foodstuff, biological products or waste materials. A cooling plate with numerous vertical holes or pores is provided at the bottom of the refrigerated tank, while a refrigerant circulates through suitable channels in the plate (Fig. 3). The slurry moving through the pores is frozen in the plate, thus providing a resistance to the movement of the incoming material. The pores in the plate open onto an evacuated refrigerated chamber, and there is a heated screen adjacent to the exit of the plate. The balance between the pressure of the slurry entering the cooling plate and heat on the opposite side of the plate regulates the flow of the material. The pressure drop is held by means of frozen plugs of material that move slowly through the pores of the chilled plate. The freeze-dried product is then removed by means of a nitrogen flux and pumped, through a Venturi arrangement, to a collection vessel. According to the preferred embodiment of this concept, the diameter of the pores in the plate is similar to the dimensions of ice crystals, and an aerosol of sublimed crystals is therefore produced, which may later be sorted or classified.

### 3.2.10. Controlling product morphology

However, a problem with the Arsem [100] freeze dryer is that the final product is dimensionally inhomogeneous and morphologically uncontrolled, thus requiring a subsequent intervention to make it powdery or granulated. Smith [98] previously described a piece of

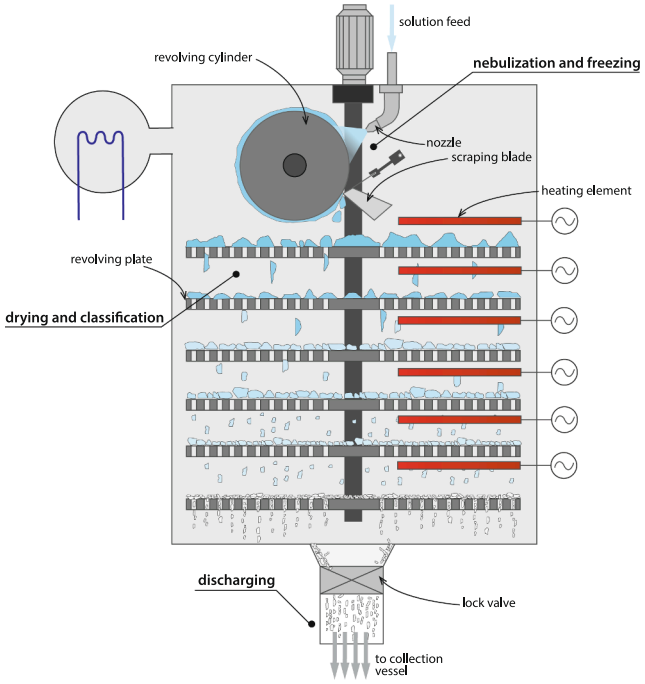


**Fig. 4.** Scheme of the continuous freeze-dryer concept proposed by Bruttini [101].

apparatus which generated a compact output material and not a granulated one. This can be considered a disadvantage, since granulated products can be controlled and treated more easily. Bruttini [101] claimed that his new apparatus could solve both of these drawbacks. He claimed that his apparatus enables a continuous control of the powdery granule size, thus at the same time avoiding mechanical actions that could damage the product. The objective is also to avoid the need for human interventions, particularly for pharmaceutical products, which could generate possible contaminations. Therefore, his apparatus comprises a drying chamber, which houses a cooled revolving cylinder, keyed to a refrigerated shaft. The material that has to be freeze dried is nebulized onto the aforementioned cylinder and frozen. The frozen material is then removed, by means of a scraping device, which makes it fall onto a series of underlying revolving planes. Each revolving plane is secured to a revolving shaft and has a circular edge and several gauged holes or through-notches. These holes and notches carry out a dimensional selection, while heating elements placed between the revolving planes provide the energy necessary for sublimation. Finally, the freeze-dried product that settles onto the lower wall of the vessel is collected in a removable vessel. A scheme of Bruttini's dryer is illustrated in Fig. 4.

### 3.2.11. Atmospheric continuous freeze-drying

In 2013, Weisselberg registered a patent pertaining to a continuous freeze-dryer that operates at atmospheric pressure [102]. Raw material, in particulate and frozen form, is continuously supplied to the drying chamber and heated by recycled air or inert gas, such as nitrogen. The chamber incorporates several vertically displaced trays, which may have apertures, thereby allowing the material to pass through or cascade downwards from one tray to the next. Trays may, for example, rotate inside the chamber and a cantilevered device may be provided to push material through the apertures as the trays rotate. Alternatively, the trays may be stationary, and the cantilevered devices may sweep across the trays. A set of fans is used to circulate the heated air or gases inside the chamber. Alternatively, or even additionally, electrical heaters or hollow tubes with flames inside may be used. The sublimated and exhausted gas is then passed through a cooling device, a particulate filter and, finally, a desiccant system, in order to maintain the partial

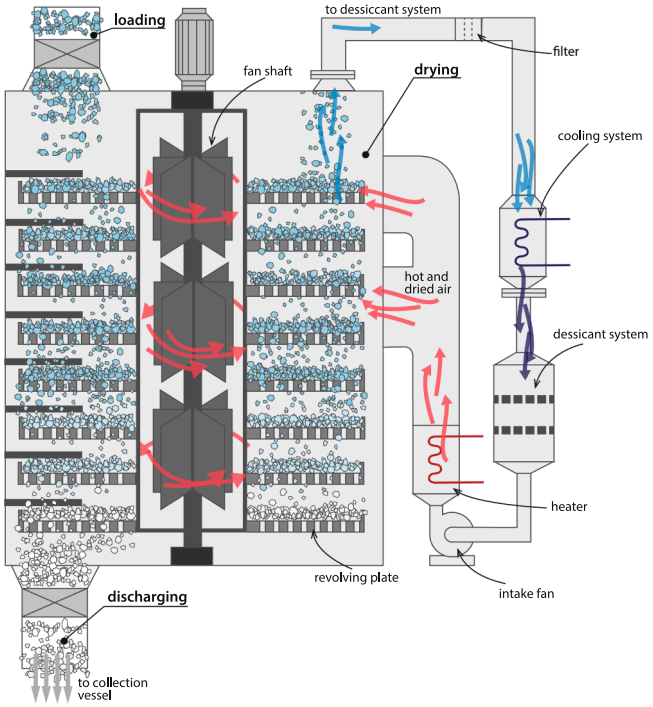


**Fig. 5.** Scheme of the continuous freeze-dryer concept proposed by Weisselberg [102].

pressure of the substance that has to be sublimed at a sufficiently low level. Another possible solution would be to introduce an extremely dry gas into the chamber. The desiccant used could be either solid or liquid, and, once saturated with moisture, it could be rejuvenated and recycled. It was also contemplated that various desiccant systems could be arranged in parallel, so that when one or more of them became spent, it could be removed from the line and rejuvenated without interrupting the process. Weisselberg claimed that this concept, schematized in Fig. 5, is suitable for both food and pharmaceutical products.

### 3.3. Progress in the pharmaceutical industry

As previously discussed, it has been claimed that some of the apparatus proposed in the patents cited so far are also suitable for pharmaceuticals, but it is also true that they were not developed explicitly to perform this function. However, parallel to the improvements in the food industry and the variety of ideas proposed in the aforementioned patents, some concepts have also been suggested specifically for the processing of biologicals.

#### 3.3.1. Application to biological materials

A continuous dryer was constructed at Fort Detrick in 1952 to dry biological materials [103]. The material is frozen in the form of pellets, using a bath of liquid Freon cooled by dry ice. The pellets are fed into the drying chamber, which consists of two Pirex bell jars, and passed through a refrigerated feeding system, mounted on top of the dryer. An inclined chute carries the frozen material from the feed inlet to a suitable hopper, mounted over one end of a belt, where a monolayer of pellets is formed. Vibrators are mounted onto the chute and onto the feed hopper to allow an easy handling of the pellets. The belt is driven by means of a variable-speed drive, and is connected, at the end of the vacuum chamber, to a chute for the collection of the dried product. The energy necessary for sublimation is supplied by means of electrical heaters, and a condenser, connected to a vacuum pump, is mounted onto the bottom of the drying chamber. This dryer has a capacity that ranges from 200 g/h to 400 g/h of frozen pellets, depending on the belt speed. It could, for example, reduce the moisture level in cultures of

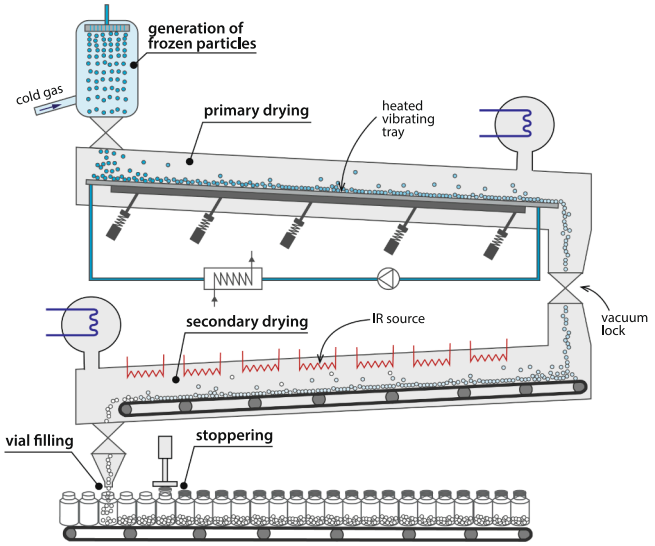


**Fig. 6.** Scheme of the continuous freeze-dryer concept proposed by Rey [89].

*Serratia marcescens* from 90% to 1% at a rate of 50 to 60 g/h of dried material, thus allowing a recovery of viable cells equal to or higher than 80%.

#### 3.3.2. Processing of small frozen granules

Some years later, Rey [89] proposed a process in which the initial solution is frozen into spherical granules of a given size. This could be done, for example, by dropping regular droplets of the liquid into a counter-current of cold air, as illustrated in Fig. 6. The granules are then loaded continuously, through a vacuum lock, onto a heated conveyor in a drying chamber. The tray may be vibrated, for example, thus inducing a continuous motion of the granules towards the dryer exit. Here, a transfer lock discharges them into a second chamber, where secondary drying is performed. In this chamber, granules may be exposed to a well-controlled infrared or microwave heating to promote desorption. Finally, the dried particles are distributed into previously sterilized vials that are then capped. Thanks to the small size of the granules, the freeze-drying times can be reduced significantly [104], and, in that dispersed form, reconstitution would be very fast. However, the application of Rey's concept to very small granules (below a millimeter) would be technically difficult, because of the risks of dust generation, clustering of granules, and of heat or mechanical damage for the product. Moreover, ensuring the sterility of the product would not be easy in the proposed apparatus, because the material would be in direct contact with the mechanical parts of the dryer, and, thus, Pisano et al. [105] proposed introducing an e-beam sterilization treatment after the freze-drying process. However, this treatment still requires further studies, as it may deactivate the active ingredients.

#### 3.3.3. Active Freeze Drying

A recent concept related to continuous freeze-drying is the so-called *Active Freeze Drying* [106]. A drawback of the conventional tray-type freeze dryer is the formation of lumps during the drying process, that is, the clustering of individual granules into one piece of material. This means that the product often has to be crushed after freeze drying, which may lead to damage of the structure of the product. Another disadvantage is the relatively low heat transfer rate, as a result of the absence of agitation. Finally, because of the complex handling of granular material in trays, dust formation is inevitable. A possible solution to these problems was suggested by the Hosokawa Micron BV company in Doetinchem, where experiments demonstrated that it was possible to operate a freeze drying process under active, mixed conditions. In the Active Freeze Dryers chamber, shown in Fig. 7, the

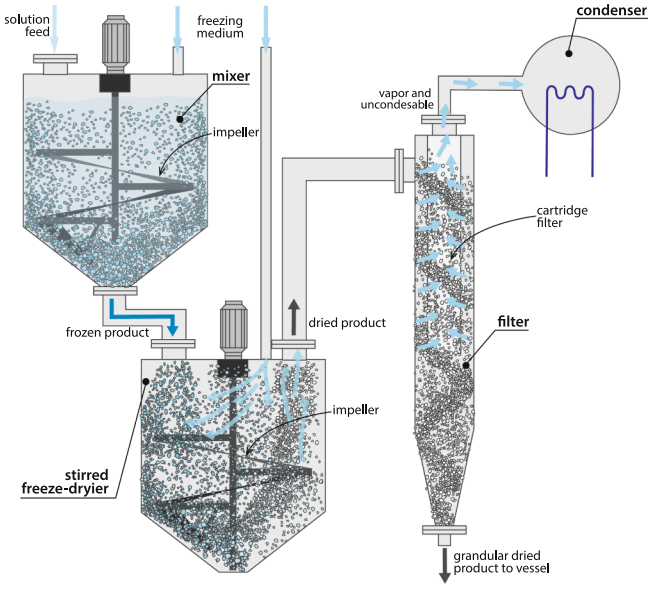


**Fig. 7.** Scheme of the active freeze-drying process [106].

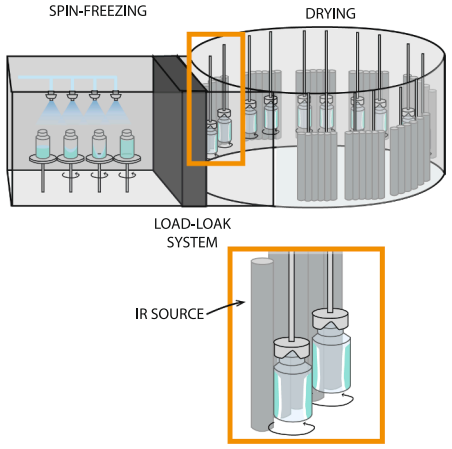


**Fig. 8.** Schematic of Corver and De Meyer's spin freezing concept [113,44].

material that has to be dried is first frozen, using a freezing medium and/or jacket cooling. After completion of the freezing step, the drying chamber is evacuated to a suitable pressure for sublimation. The heat necessary to remove the water is supplied through a jacket and distributed throughout the frozen granules by means of a stirring motion. Removal of the connecting ice structure within the frozen material will lead to a reduction in size, thus, at the same time, preventing the formation of lumps. Compared to traditional tray-type lyophilizers, Active Freeze Dryers guarantee a superior heat transfer rate, due to the continuous mixing of the granular frozen product. This can substantially reduce the drying times. Moreover, handling operations are simplified and there is no need for additional crushing of the dried product. This simplification of handling operations results in reduced risks of contamination, thus making Active Freeze Drying suitable for aseptic and sterile operations. Even though the main applications of Active Freeze Drying are in the pharmaceutical industry, other fast-growing markets are those of nanomaterials and foodstuff. However, some problems still needs to be addressed. First, because of the reduction in the amount of solvent, the level in the drying vessel gradually decreases, thus slowing down the sublimation process. This could be compensated for by continuously topping up the vessel with new material. Secondly, a dried dust is often ejected from the sublimating material, and a filter has to be used to separate the dust from the material.

### 3.3.4. *Fine-Spray Freeze Drying*

Ulvac has recently developed a new freeze-drying process, the so-called Fine-Spray Freeze-Drying, in which a liquid is sprayed directly into a vacuum chamber through special nozzles, self-frozen and deposited on a heated shelf, where the drying process is carried out to generate micro-particles. In contrast with bulk lyophilization, where the extension of the sublimation interface is limited, the extremely larger surface-to-volume ratio of sprayed droplets results in remarkably faster freezing and drying rates, because of the enhanced heat and mass transfer. For instance, it was estimated that spraying 1 ml of solution in 0.5-mm droplets produces a surface area that is about 80 times larger than the corresponding liquid-gas interface in a 14- mm diameter vial. [107] The self-freezing and drying processes are therefore extremely fast, and a uniform particle size distribution can be obtained, with no need for a further crushing process. Moreover, the apparatus is fully-closed, thus guaranteeing sterile conditions. Azbil Telstar Technologies has a cooperation agreement with Ulvac for the development of the

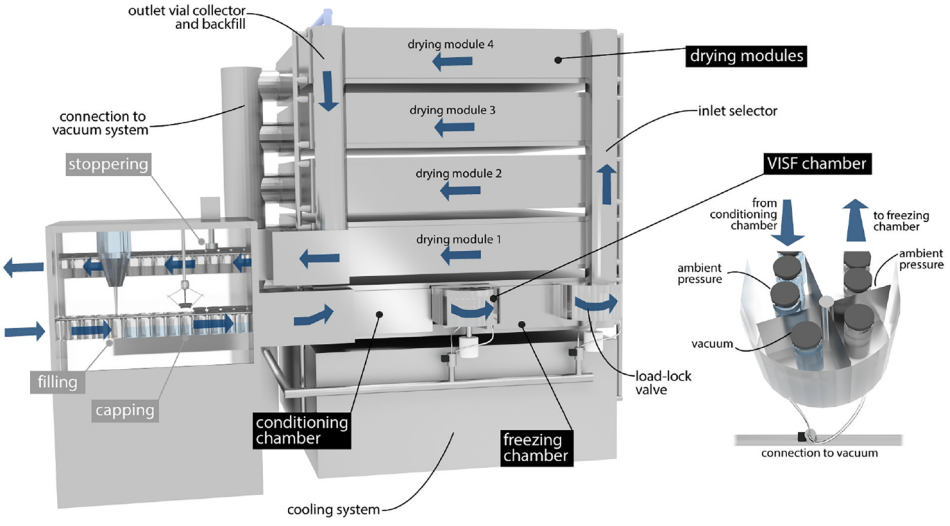


**Fig. 9.** Continuous freeze-drying of suspended-vials [115].

**Table 1**
Summary of the continuous freeze drying technologies presented in this work. For each of them, the year of application/presentation, key features, application, main benefits and drawbacks are listed. For the technology that are not currently being used, and for which a possible application was not suggested by the inventors, the indication 'not specified' has been used in the Application field.

| Year | Technology | Key Features | Application | Benefits | Drawbacks |
|---|---|---|---|---|---|
| Freeze-drying of bulk material | | | | | |
| 1952 | Rhian et al. dryer [103] | Liquid raw material, belt conveyor | Biologicals | Fast drying | Fast freezing not suitable for all materials |
| 1966 | Fuentevilla dryer [91] | Frozen raw material, vibrating trays, moisture control | Foodstuff, biologicals, pharmaceuticals | Easy design | Slow drying |
| 1966 | Vigano dryer [92] | Liquid raw material, freeze-drying occurs over the container inner surface | Not specified | High production rate | Risk of mechanical damage |
| 1966 | Togashi and Mercer dryer [93] | Liquid/solid raw material, limited vapor velocity, vibrating trays | Not specified | Rapid drying | Risk of mechanical damage |
| 1967 | Rockwell et al. dryer [94] | Frozen liquid/solid raw material, feeding screw, rotatable drum | Foodstuff | Minimum mechanical damage | Difficult dosage |
| 1971 | Oetjen et al. dryer [96] | Frozen raw material, vibrating screen conveyors, comminution inside drying chamber | Not specified | Avoided product thawing | Risk of mechanical damage |
| 1971 | Smith dryer [97] | Pressure roll and back-up roll to exert pressure on the frozen powder | Not specified | Avoided release of loose particles, increased conductivity of the product layer | Risk of mechanical damage |
| 1972 | Mercer et al. dryer [95] | Liquid raw material, vibrating conveyor, bouncing motion | Food and biologicals | Quick freeze-drying | Difficult dosage |
| 1973 | Smith dryer [98] | Liquid/semiliquid raw material, compact output material | Bot specified | Avoided release of volatiles | Difficult dosage and handling of output material |
| 1973 | Gottfried dryer [99] | Liquid raw material, screw conveyor | Food and biologicals | Possibility to monitor drying end | Risk of mechanical damage |
| 1986 | Arsem dryer [100] | Slurry raw material, pressure drop provided by the freezing of supplied material | Foodstuff, biologicals or waste materials | Efficient generation of vacuum | Morphologically and dimensionally inhomogeneous product |
| 1993 | Bruttini dryer [101] | Liquid raw material nebulized and frozen on revolving cylinder, revolving planes for drying | Pharmaceuticals | Control of granule size, avoided mechanical damage | Low conductivity of granules |
| 2010 | Rey dryer [89] | Liquid raw material, heated conveyor, homogeneous granular output | Pharmaceuticals | Fast drying, fast reconstitution time | Difficult control of sterility |
| 2013 | Weisselberg dryer [102] | Particulate frozen raw material, atmoshperic pressure, desiccant system | Food and pharmaceuticals | Reduced process cost at atmospheric pressure | Lower sublimation rate at atmospheric pressure |
| 2015 | Active freeze drying [106] | Liquid raw material, stirring motion during drying | Pharmaceuticals, nanomaterials, foodstuff | No clustering of granules, effective heat transfer | Inconstant sublimation rate during the process, dust formation |
| 2015 | Fine-Spray freeze drying [108] | Liquid raw material, self-freezing of sprayed liquid, generation of dried micro-particles | Pharmaceuticals | Fast process, uniform particle size, sterility | Technology still under development |
| 2017 | Dynamic Freeze-Drying [109] | Flowable raw material, rotational lyophilizer, gentle mixing | Pharmaceuticals | Homogeneous, dust-free material, fast drying | Still not continuous |
| Freeze-drying of unit doses | | | | | |
| 1957 | Becker dryer [110] | Spin freezing, guide capsules to transport vials | Pharmaceuticals | Fast freezing, accurate dosage | Traumatic journey of vials, limited productivity |
| 1965 | Broadwin dryer [111] | Spin freezing, two-stages dehydration | Pharmaceuticals | Suitable for heat sensitive liquids | Low throughput |
| 1978 | Braun dryer [114] | Push-pull device, automatic filling/sealing | Pharmaceuticals | Minimum risk of contamination | Complicated design |
| 1999 | Oughton et al. dryer [112] | Spin freezing, roller conveyor, automatic filling/labelling | Pharmaceuticals | High throughput | Complicated design |
| 2012 | Corver dryer [113] | Spin freezing, endless belt, radiative sublimation | Pharmaceuticals | High throughput, easy scale-up | Formation of a large ice-water interface, possible formation of hot spots during drying |
| 2019 | Suspended Vial Freeze-Drying [115] | Suspended-vial configuration, radiative sublimation | Pharmaceuticals | Fast sublimation rate, possible control of crystal/pore size | Technology under development |

**Table 2**
Comparison of the various freeze-drying technologies described in the present work.

| | Throughput | Footprint | Dust issues | Sterility control | Dosage accuracy | Quality control | Scale-up issues | Operation flexibility |
|---|---|---|---|---|---|---|---|---|
| Batch continuous | ↓↓ | ↓↓ | ↑ | ↑ | ↑↑ | ↓ | ↓↓ | ↓ |
| Bulk material | ↑↑ | ↑↑ | ↓ | ↓ | ↓ | ↑↑ | ↑ | ↑↑ |
| Unit doses | ↑↑ | ↑↑ | ↑↑ | ↑↑ | ↑↑ | ↑↑ | ↑ | ↑↑ |

Fine-Spray Freeze-Drying device. Telstar is in fact working on a further development of the Ulvac concept for a continuous process to be used for pharmaceuticals [108].

#### 3.3.5. Dynamic Freeze Drying

Another freeze drying technique, which is still not continuous, but very close to it, is the Dynamic Freeze-Drying technique [109]. In the concept by MERIDION, flowable bulkware is freeze-dried in a rotational lyophilizer, under constant gentle mixing. The heat necessary for sublimation is provided by means of radiating devices and surfaces at a controlled temperature. The advantages of this approach are that a homogeneous, dust-free material is produced, due to constant mixing, and a consistent reduction in drying times is obtained.

## 4. Continuous freeze-drying working on unit-doses

Freeze-dryers that work directly on unit doses, as previously stated, allow an easy control of sterility to be achieved, as well as an accurate dosage of the APIs. These represent significant advantages from the viewpoint of pharmaceutical processes. In fact, most of the existing pharmaceutical freeze-dryers belong to this category, but they are, at present, operated in batch-wise mode, and their convertion into continuous mode is not straightforward. Thus, only a few concepts have been developed for continuous freeze-dryers working directly on unit doses.

### 4.1. Shell/spin freezing and vacuum drying

A series of patents which apply the so-called shell-freezing or spin-freezing method to the lyophilization process have been registered. During freezing, the vessel containing the liquid raw material is rotated, so that the resulting product forms a thin coat or shell on the inner surface of the vessel. Various technological solutions have been proposed as shown hereafter.

#### 4.1.1. Becker's concept

In 1957, Becker [110] proposed a continuous freeze-drying apparatus, in which each vial is transported by means of a guide capsule. The liquid inside the vial is first frozen while being rapidly rotated under vacuum conditions. Subsequently, the guide capsule releases the vial into a drying chamber, and goes back to collect another vial. The vials are rolled down under gravity in the drying chamber, which consists of a long, winding heated conduit.

#### 4.1.2. Broadwin's process for heat sensitive liquids

Another continuous freeze dryer that uses the shell-freezing approach was suggested by Broadwin in 1965 [111]. A freeze drying apparatus which is suitable for heat sensitive liquids, such as enzymes and serums containing living cells, is described in this patent. The objective is to provide a vacuum dehydration method for these materials, without the use of refrigerants, to ensure a maximum survival of the living cells. The apparatus comprises a vacuum chamber, where a centrifuge with supports for the bottles holding the material to be dried is provided. As a result of the motion produced by the centrifuge, the liquid is spread over almost the entire internal surface of the bottle, thus producing a shell-shaped form. The liquid is then frozen during cooling, which is produced by evacuation of the chamber by means of a vacuum pump. The dehydration of the heat sensitive liquid is subsequently provided in two stages. The first one is accomplished during the freezing step, which is stopped when the temperature drops below −15 °C, in order to prevent the cells from being damaged. At this point, the centrifuge is stopped, heat is applied directly by conduction to the bottles in order to evaporate any of the liquid that has not been frozen, and finally the frozen shell is dehydrated completely at −50 °C. This second drying stage could also be accomplished in a separate apparatus.

#### 4.1.3. Oughton's freeze-dryer for pharmaceuticals

In the process proposed by Becker [110], vials experience a traumatic journey in the drying chamber, and there is a risk of the frozen product being disrupted. Moreover, as only one vial can be introduced at a time into the drying chamber, productivity is limited. The concept by Broadwin [111] does not allow a high throughput either, since both the freezing and drying processes are accomplished within the same chamber. Therefore, in 1999, Oughton et al. [112] proposed a new freeze-drying process with the aim of solving these problems, reducing the drying time and minimising the risk of contamination. According to the inventors, the new technology should be particularly advantageous for pharmaceutical products, such as antibiotics, drugs, enzymes, serum and vaccines. In this apparatus, the vials are first either manually or automatically loaded upside-down into the equi-spaced apertures of a magazine. The magazine is then transported, by means of a roller conveyor, to a second zone, where the vials are washed both inside and outside and sterilized using hot air. The magazines are then carried to the filling and freezing section. Here, the vials are removed from the magazines by a robot arm, rotated to a horizontal position and filled while being rotated. Freezing is then achieved by injecting a controlled flow of inert gas into the vial. This offers the advantage of speeding up the process, but, alternatively, the freezing gas could also be circulated around the outside of the vial. The speed of rotation has to be controlled in order to guarantee the formation of a shell of substantially uniform thickness, and the weight of the vials is measured before and after filling to check that the correct dosage has been dispensed. At the end of the freezing step, the spinning is stopped and the vials are returned to the magazine and transported to the vacuum tunnel, through an air lock chamber. Heater blocks in the vacuum tunnel are used to provide the energy necessary for sublimation. These heating devices were designed to direct heat radially inwards to the frozen shell material, thus substantially speeding up the drying process. Moreover, the desired temperature profile could be obtained by setting different heating blocks along the vial pathway at different temperatures. After the drying step, the vials reach a plugging zone or, as an option, a capping and labelling zone.

#### 4.1.4. Spin freezing concept by Corver and De Meyer

A recent approach has been introduced by Corver in a patent dated 2012 [113]. The continuous freeze-drying concept proposed by Corver, and then investigated in depth by De Meyer et al. [44], starts with a continuous freezing step, i.e., the so-called spin freezing, where vials, filled with a liquid formulation, are rotated rapidly along their longitudinal axis. The cooling and freezing of the solution are provided by a flow of sterile gas at a controlled temperature around the rotating vial. Consequently, the resulting frozen product is spread over a vial surface

that is larger than that of traditional freeze-drying. An appropriate load-lock system is used to transfer the frozen vials from the continuous freezing unit to the continuous drying one. Two drying chambers, for primary and secondary drying, respectively, are provided. In each drying chamber, an endless belt, with pockets to hold the vials, allows the vials to be transported, while the heat required for sublimation and desorption is supplied either by radiation or conduction. Finally, a condenser system is used to continuously remove the sublimed solvent. Since the frozen product is spread over a very large vial surface, and thin product layers are produced, De Meyer et al. [44] showed that, for some products, the total process time can be reduced by a factor of 10–40. The scale-up of this process could be achieved simply by adding parallel lines to the continuous freeze-drying modules. A schematic is shown in Fig. 8.

### 4.2. Conventional freezing followed by vacuum drying

Other pieces of apparatus that work with unit-doses and which do not use the spin-freezing approach have been proposed over the years. For example, in 1978, Braun [114] proposed a continuous freeze-dryer, in which a metal or plastic film is first formed in containers, for example, deep-drawn cups, of any desired shape. These containers are then filled with the solution that has to be freeze-dried, and moved through primary and secondary freezing sections. The depth of fill of the frozen material is checked, and containers with unsuitable amounts of material are removed from the processing line. The cups with frozen material are then moved, through air locks, towards the primary and secondary drying zones, and, finally, to the dryer exit, where a covering film or foil is used to seal the containers. The advancing movement along the apparatus is provided by a push-pull device, connected to the air locks, while vacuum pumps and condensers are used to provide the low pressure required for sublimation and for the removal of water vapor. Backup condensers are also provided to allow continuous operation of the system, even when the primary condensers need to be defrosted. The heat required for sublimation is supplied either by circulating brine, or by electrical devices. In another possible set up, raw material is packed into bottles, which are also provided with stoppers. Subsequently, these bottles are moved to the freezing and drying sections, but in this case, instead of the formed foil or film web, a conveyor belt is used. At the dryer exit, a stopper inserting device, which consists of a pressure plate driven by a hydraulic cylinder, forces the stoppers into the bottles. This is accomplished in a moisture-proof manner, to avoid absorption of water from the ambient air. Finally, the bottles are transported to a capping machine, where they are provided with screw caps. The step-wise advancement is again provided by a push-pull device, which is connected to the air locks that separate the different sections of the apparatus (Fig. 9).

### 4.3. Suspended-vial configuration as a possible approach to continuous freeze-drying

Finally, our research group has recently proposed a new continuous freeze-drying concept, that works with unit-doses [115]. In this apparatus, the vials are suspended over a track and move continuously through chambers where different pressure and temperature conditions are maintained. In the first section of the dryer, the vials are filled continuously with a controlled amount of liquid, and are then moved to the freezing zone. The freezing of the initial solution may be achieved using either spontaneous nucleation, or controlled nucleation by means of vacuum-induced surface freezing (VISF) [81,82]. In the first case, vials are simply cooled down, until complete solidification has taken place. In the second case, VISF is carried out continuously using three modules connected in series: the conditioning module, where the product is equilibrated at the desired temperature, above the onset of ice nucleation; the nucleation module, where the pressure is lowered to induce nucleation in the product; and finally the freezing module, in which complete solidification of the product is achieved using a low temperature. In the freezing section, cooling may be accomplished by either natural or forced air convection, and by radiation. Moreover, the heat transfer rate may be controlled by adjusting both the temperature and the flow rate of the cooling gas. The suspended-vial configuration used in this apparatus has the advantage of significantly reducing the temperature gradients within the product being frozen, thus resulting in much larger and more uniform pores within the product, compared to conventional batch freezing. This allows a much faster sublimation rate, thus speeding up the primary drying phase and reducing the total cycle time. Furthermore, the precise control of nucleation temperature, as obtained by VISF, reduces the vial-to-vial variations in ice morphology and hence in the porous structure of the final dried product. After completion of the freezing step, the vials are moved to the primary and secondary drying chamber, through a sluice-gate system. Here, removal of water by sublimation and desorption is achieved using low pressure, while the heat required for the process is mainly supplied by radiation. A vacuum system, composed of a condenser and vacuum pump, is used to guarantee the desired pressure, while the temperature of the radiating surfaces is controlled by circulating a heat transfer fluid. In this configuration, all the vials are exposed to the same heat and mass transfer conditions, thus avoiding problems of inhomogeneity which represent a major drawback of the batch process. Finally, a further advantage of the present approach is the remarkable reduction in the total cycle time by a factor of 10 times [115]. For instance, it has been estimated that it would take approximately 51 h for drying a 5% w/w sucrose solution in 2 ml vials if using a batch configuration: 10 h for loading, 5 h for freezing, 18 and 8 h for primary and secondary drying, respectively, and 10 h for post-cycle operations (unloading, defrosting, cleaning in place etc.). The same cycle would only require about 6 h in a continuous plant working with the suspended-vial configuration, because the loading, unloading and secondary drying phases would not be necessary any more, and only 0.5 and 5.5 h would be needed for freezing and primary drying, respectively. [115] In fact, suspended-vial drying can be carried out at a low pressure, thus maximising the mass transfer rate without compromising the heat transfer. The apparatus uses different modules in parallel which can regulate throughput and output products from different upstream feeds having different formulations. Moreover, alternative dosage forms, such as granules [116] or innovative packagings such as double-chamber cartridges and syringes can be also processed. A summary of the technologies discussed in the present work is provided in Table 1.

## 5. Conclusions

In this work, an organic overview of the continuous freeze-drying concepts proposed over the years has been provided. Although freeze-drying in the food industry is, in most cases, carried out continuously or semi-continuously, in the field of pharmaceuticals it still remains a batch process. This delay in the pharmaceutical industry is due to the difficulty of ensuring, during continuous operation, the strict requirement of sterility and the accurate dosage of the APIs that are necessary for pharmaceutical products. However, the shift towards continuous production would lead to several benefits, as summarized in Table 2. In fact, continuous processes would result in a significantly increased throughput and a smaller footprint, together with an improved process and quality control and greater flexibility. Moreover, the scale-up process would be easier. In the case of continuous freeze-dryers working on bulk material, some problems related to dust formation and/or volatile release could arise during production, while in batch freeze-dryers, dust generation might only occur during the handling operations that precede and follow the cycle. On the other hand, continuous freeze-dryers working on unit doses would make it possible to avoid issues due to dust formation. Furthermore, a further advantage of dryers working on unit doses, unlike bulk material, is the easier control of sterility, and the more accurate dosage of the APIs. In a continuous

facility working with unit doses the risk of contaminations due to manual handling of the product pre- or post-lyophilization would be eliminated, thus making this technology even more promising than the current batch approach from the point of view of sterility control.

Table 2 suggests that the shift to continuous production would be advantageous, from the point of view of both process efficiency and product quality. Therefore, future work should be aimed at developing a continuous freeze-drying process that would be suitable for pharmaceuticals. The achievement of such a process would lead to a remarkable saving of time and money as well as to an improved quality and homogeneity of the final product, thus proving beneficial for both the industry and the patients. The main objective of this work has been to provide a solid background on this subject, which may serve as a starting point for future research.

## 6. Disclosure statement

R. Pisano, L.C. Capozzi and B.L. Trout have developed one of the technologies described in the present work, for which a patent is also involved. However, the different technologies herein reviewed have been described on an objective basis, and our statements have rigorously been based on scientific data.

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