Spray freeze-drying for Formulations of Precision Medicine & Vaccines

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The majority of the novel highly potent drugs, developed on the basis of modern molecular medicine, taking into account cell surface recognition techniques for precision medicine, are often thermo-sensitive and have poor water-solubility. A substantial increase of drug solubility can be obtained by the formulation of nanocomposite pellets using a spray freeze-drying process, which was originally developed at the University of Basel. This process was successfully commercialized by the company Meridion (meridion.de) of Dr B. Luy. This platform, among others, can be used for manufacturing vaccines, biosimilars, biologics, monoclonal antibodies, antibody-drug conjugates for precision medicine. In this context, it is important to keep in mind that in case of a vaccine formulation the double chamber syringes can be kept at room temperature and do not need to be stored at –77°C. In addition, this platform can be used for medications based on the phage therapy to treat antibiotic resistant (MRSA) bacterial infections. In this context, a specific phage having the property of a virus only infects the bacterial cells. Thus, the infected bacteria cell loses its negative function and starts to serve as a host cell for the replication of more «friendly» viruses. Such an approach is also used for a viral therapy of cancer cells which will lead to cancer therapy without the side effects of traditional chemotherapy and radiation treatment. This type of highly specific targeted medication is the future of precision medicine. At the same time, it can be predicted that this innovative spray freeze-drying technology will be the future of manufacturing lyophilized products.

1. Spray – Freeze-drying as a Method of Choice for a safe Manufacturing and Handling of Nanoparticles and Nano Composites

1.1. Rationale of this Approach

The classical freeze-drying process (Freeze-drying – Wikipedia) in a traditional vial has a lot of limitations due to the fact that the liquid is directly frozen and dried in the vial, leading to heat transfer problems as shown in Fig. 1.1. This energy transfer depends on the local temperature of the vials on the shelf, which explains that the cake may show cracks **(Patel et al 2017)** and is not perfect as in Fig. 1.2. Therefore, the company Seidenader (https://www.seidenader.de/en/inspection/our-technologies/) offers automated inspection, to test each sample and to discard vials with defective cakes. Besides product sterility, the most critical parameter is the residual moisture content of the lyophilized product. For this reason, the company Roche uses an in-line residual moisture determination for a complete batch inspection of lyophilized end products **(Sukowski L 2017,** Fig 1.1). From an ethical point of view, a 100 % inspection of all vials means that the company really takes care of the patients.

On the other hand, the necessity of a 100 % inspection shows that the classical freeze-drying process is not an optimal method. Fig. 1.3 shows a vial containing mono-sized pellets obtained by the spray freeze-drying process, the future method of choice.

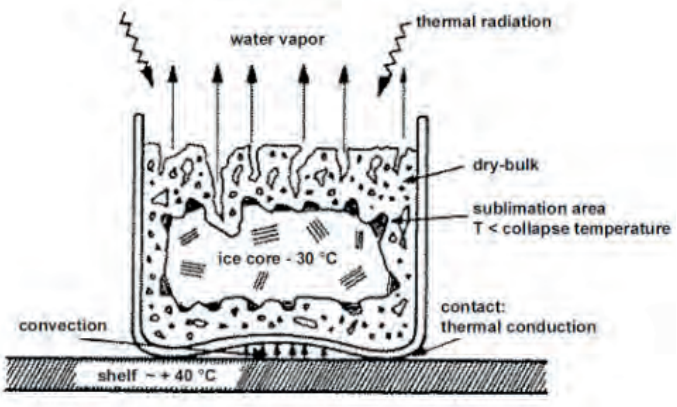

Fig.1.1: Heat transfer and vapor transport in the vial. (Courtesy Sukowski L 2003)

Fig.1.2: Vial with intact cake. (Courtesy Meridion)

Fig.1.3: Vial with mono-sized pellets obtained by Spray Freeze-drying. (Courtesy Meridion)

In the context of Fig. 1.1 it is important to realize that the control of the primary freezing step is most essential regarding the final quality of the lyophilized product. In the case of classical freeze-drying of the vials on shelves (Fig.1.1) this step is very critical since the pharmacological activity of the biological product is a function of the speed of this initial freezing step and of the formulation. Thus, the ultra-fast freezing step of the MERIDION technology has decisive advantages for obtaining the targeted optimal activity of the biological being close to 100 %. This fact impressed specialists in classical freeze-drying attending the 2019 AIChE Annual Meeting in Orlando listening to the MERIDION presentation «Advances in Spray-Freeze Drying for Uniform Bulk Intermediates and Lyo Products» **(Leuenberger H 2019b).**

2. Implementation of the Spray Freeze-drying concept by Meridion.

2.1. Technology Development Background

Started in 1980's in cooperation with Glatt AG (Switzerland) the PhD candidates Alain Kahn **(Kahn – Wyler A H 1987)**, Marco Mumenthaler **(Mumenthaler M 1990)**, Hans-Peter Mennet **(Mennet HP 1994)** and Mathias Plitzko **(Plitzko M 2006**) evaluated the conditions, which should allow the manufacture of drug formulations which show as solid dosage forms a high stability and an instant solubility to be used in case of low water-soluble drugs for sterile injections, for capsule formulations and for instant-drink solutions. Thus, this novel technology has the potential to replace the classical freeze-drying process. Alain Kahn was the first to show the feasibility using this process, Marco Mumenthaler was the first who showed that it is possible to manufacture instant soluble coffee powder without losing the original flavor, i.e., there was no need first to collect the aromatic flavors in the classical freeze-drying process and to add the flavor subsequently to the product. Matthias Plitzko was the first who was able to manufacture mono-sized pellets with this novel process. The work of the PhD students led among others to the US patent 6, 584, 782 B2, July 1, 2003 as part of the 12 patent families of the Glatt Group with the name Hans Leuenberger as inventor **(Leuenberger H, Prasch AKT, Luy B 2003).** However, the patent based on a quasi-continous process separating the spray-freezing step from the subsequent drying processes was not implemented by the Glatt group despite the fact that the US patent already proposed to separate the freezing and the drying process. Ergo, the process line consisted of three towers taking care of the instant freezing step at $T_{AIR} < -60°C$ in the fluidized bed (FB) tower Nr. 1, of the primary drying phase at $T_p < -10°$ C in the subsequent FB tower Nr. 2 and of the secondary drying phase at T_s = ambient temp. in the FB tower Nr. 3. As already shown by Alain Kahn, Marco Mumenthaler and Hans-Peter Mennet, a single pot process is not the solution. Thus, Meridion Technologies succeeded in commercializing the spray freeze-drying technology using two steps, a) the instant freezing process for the formation of nano composite pellets in a separate tower and b) as a second innovative step a dynamic bulk drying process using a rotary drum based on the patent US 20140230266 A1, 2014 for the production of freeze-dried particles. Thus, the company Meridion could avoid the use of fluidized bed processes for commercializing the spray freeze-drying process.

Prof. Hans Leuenberger

Hans Leuenberger studied experimental physics resulting in a PhD in nuclear physics at the University of Basel. He worked for twelve years at Sandoz (today Novartis) before he was elected as a full time professor in Pharmaceutical Technology at the University of Basel. He served as Dean of the Science Faculty, as President of the Scientific Council of the Swiss Academy of Engineering Sciences SATW and as Vice President of SATW. He received numerous awards (www.ifiip.ch/awards gallery), and was Visiting Professor of the Grand Ecole des Mines, Albi, France (https://www.imt-mines-albi.fr/en/imt-mines-albi) being Member of its Advisory Board 2001–2006. He is Honorary Member of SATW (www.satw.ch), of the Society of the Swiss Industrial Pharmacists (SSIP) (www.gsia.ch), Corresponding Member of the Royal Academy of Pharmacy of Spain, Foreign Member of the Russian Academy of Engineering; Fellow of the Swiss Academy of Pharmaceutical Sciences and Fellow of the American Association of Pharmaceutical Scientists (AAPS). After moving to Florida he is Member of the Adjunct Faculty of the College of Pharmacy of the University of Florida. Lake Nona Campus, Orlando.

2.2. Spray Freezing: The Generation of homogeneous frozen bulk

At an ambient-pressure, frozen microspheres are generated by dispersing the substrate liquid, using frequency nozzles, into single droplets, which by gravity pass through a cooling zone, congealing to frozen spheres.

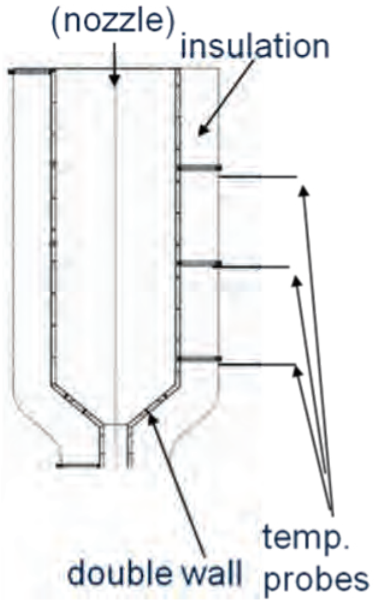

Fig. 2.2.1: Scheme of Spray-freeze Chamber. (Courtesy Meridion)

Fig. 2.2.2: Spray-freeze Lab Unit. (Courtesy Meridion)

The mono-sized droplets are sprayed into the processing gas, which is cooled by the double wall with liquid or gaseous nitrogen in the temperature range of –77°C to –140°C. Thus, the droplets are immediately frozen, which is important for the stability of biologicals. This is an important asset compared to the classical freeze-drying process as confirmed by other speakers at the AIChE 2019 meeting in Orlando **(Leuenberger H, 2019b).**

2.2.1 Droplet generation by controlled laminar jet break

Matthias Plitzko **(Plitzko M, 2006)** used first, in his PhD thesis, a special prilling nozzle, which allowed him to generate mono-sized droplets as an example with a diameter d_d of 270 µm. The diameter is a function of the nozzle diameter D_n, throughput SR (ml/min), and the frequency f of the unit (Fig. 2.2.1 Table 2.2.1), which is needed to create a controlled laminar jet break.

D_n (nozzle) [µm]	d_d (droplet) [µm]	SR (spray rate) [ml/min]	f (frequency) [Hz]
150	270	2.8	3072
200	330	7.0	2720
300	480	10.5	2030
400	610	10.5	860

Table 2.2.1: The correct choice of the operating parameters (D_n, SR, f) is crucial to avoid the coalescence of the droplets of the diameter d_d **(Plitzko M, 2006).**

Fig.2.2.3: Stream of droplets. (Courtesy Meridion)

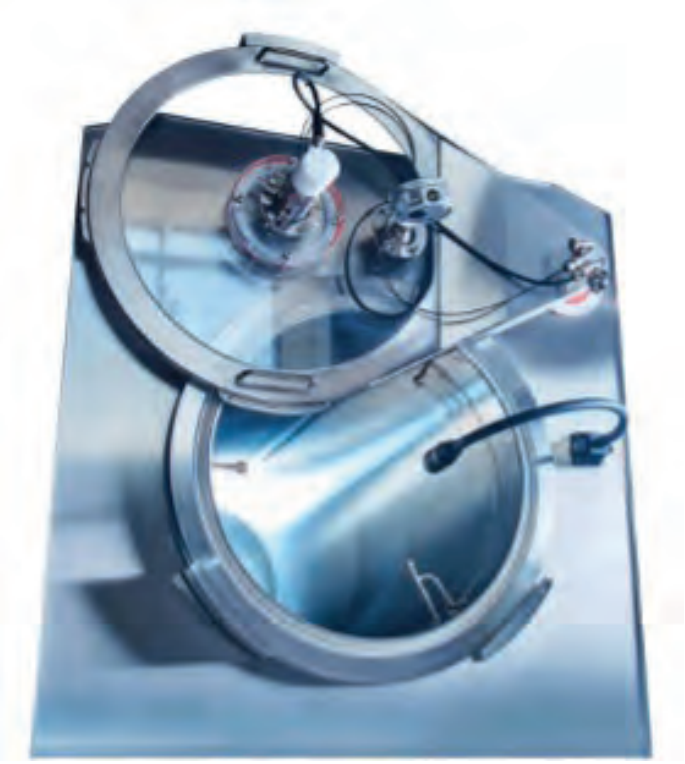

Fig.2.2.4: Top Lid with Spray Nozzle of the Spray-Freeze Chamber. (Courtesy Meridion)

Fig.2.2.3 shows the separation of the droplets in the spray freeze chamber and Fig. 2.2.4 is the photo showing the top lid with the spray nozzle. For the separation of the droplets and for avoiding the subsequent coalescence the droplets need to be charged with the same polarity. This is the function of the high voltage cathode of Fig. 2.2.5.

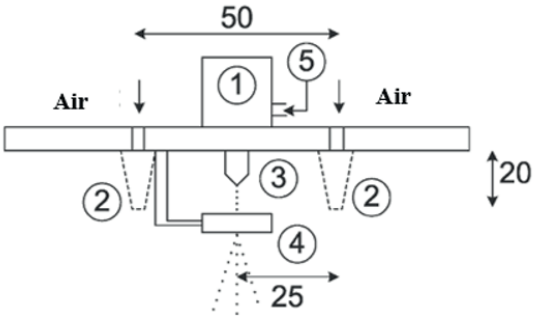

Fig. 2.2.5: Scheme of the Prilling Spray Nozzle: ① prilling control device for the separation of the droplets; ② Air flow; ③ Nozzle with the diameter D_n; ④ Cathode (1.1-1.8 kV) ⑤ Spray rate SR (material flow, ml/min). (Courtesy Plitzko M, 2006)

As an alternative of using an electrode, MERIDION has developed a gas-based deflection technology to avoid electrostatic charges which could interfere with product handling requirements. In addition, it has to be kept in mind that a minimum amount of the solid content of the spray solution is needed that the freeze-dried droplet is stable and keeps its shape. Thus, if the final porosity of the product is too high, the pellets will not be mechanically stable and will disintegrate into smaller particles. This statement is related to the fact that the amount of solid content dissolved needs to percolate the droplet. On the other hand, a high porosity is desirable of such nanocomposite particles since the high internal surface of the pellets is an important quality attribute for the instant solubility of the formulations in case of drink solutions or for parenterals. Needless to say that an aseptic process is a prerequisite for manufacturing sterile parenterals.

2.3. Dynamic Bulk Freeze-drying: The Lyophilization of frozen bulk

The frozen bulk ware is lyophilized in a rotational vacuum freeze-dryer under constant gentle mixing and at low pressure such as 20 µbar which is used in a classical freeze-dryer. Sublimation energy is transferred by radiation and temperature-controlled surfaces. In this context this process only differs from the well-known classical principle by the rotational movement of the material to be lyophilized. This is, however an important innovation since the movement of the material leads to a homogenization of the freeze-drying conditions. Thus, this innovation resolves the problem of the classical freeze-drying dishes which are cooled to –55°C for the freezing of the solution in the vial and which are subsequently used, e.g., at a temperature of +55°C, for supplying enough energy (heat) to the frozen solution to induce and sustain the sublimation process. Unfortunately, this energy transfer may depend on the location of the vials (Fig. 1.1) on the table/shelf. A similar problem exists in case a microwave oven. Uneven heating in microwaved food can be partly due to the uneven distribution of microwave energy inside the oven. Thus, this problem can be reduced by by a turntable or carousel that turns the food in the **microwave oven** (Wikipedia). In case of the dynamic bulk freeze-drying process the material is gently mixed in the rotating drum with a controlled surface temperature. The heat transfer from the surface of the drum to the pellets results from silicon oil circulating in a double wall of the drum. The silicon oil can be adjusted in the range from –55°C to +55°C . To be on the safe side, the dynamic bulk freeze-drying process uses infrared radiation for the optimization of the heat transfer needed for the removal of water by sublimation. It is evident that the mechanical stability of the dried pellets depends on the concentration of dissolved solid formulation. The solid material in the solution needs to percolate the 3D volume of the pellet **(Holman LE. Leuenberger H, 1990).** Thus, at very low concentrations the final porosity of the pellets would be too high and the nanocomposite pellets would mechanically disintegrate into finer components. This is not the goal of nanocomposite pellets since nanocomposite material has a reduced surface activity and as a result a better storage stability as nanoparticles. In the optimal case the pharmaceutical nanocomposite pellets disintegrate into nanoparticles in the stomach after oral administration, which is an important advantage in case of low water-soluble drugs **(Leuenberger H, 2002).**

Fig. 2.3.1: Laboratory dynamic bulk freeze-drying unit. (Courtesy Meridion).

2.4. From laboratory to manufacturing scale

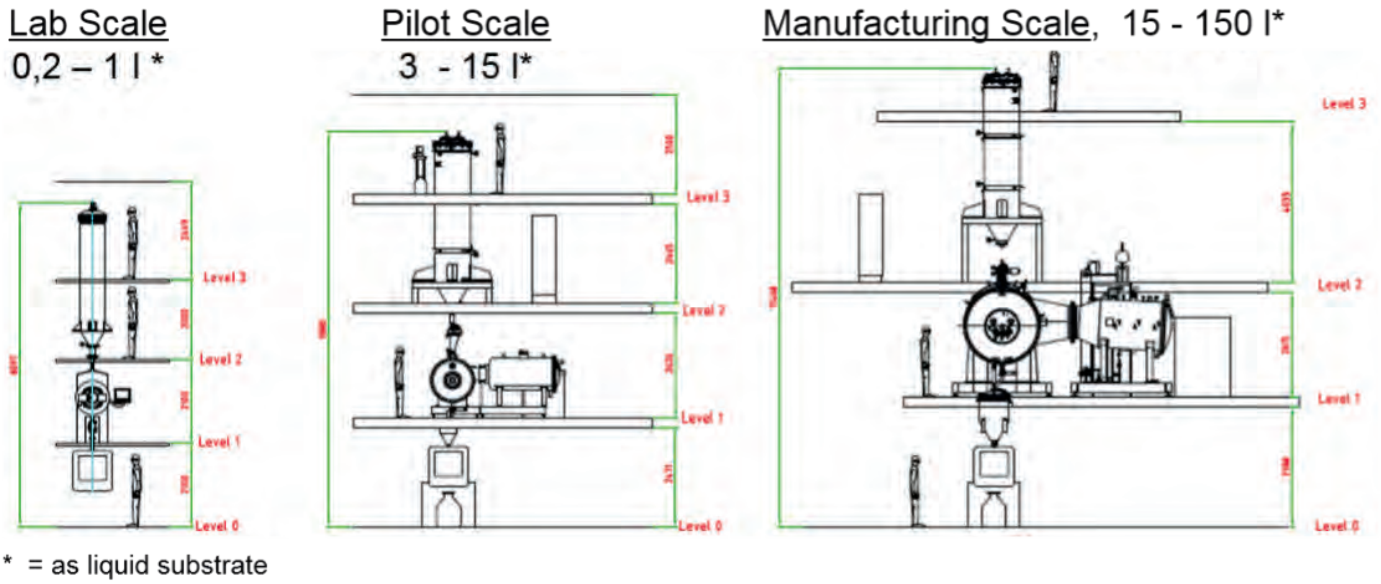

Fig. 2.4.1: Process lines from laboratory to manufacturing scale. (Courtesy Meridion)

In conclusion, the innovative spray freeze-drying technology leads to dust-free nanocomposite pellets, which can be safely handled. The resulting pellets show a high homogeneity and quality. Thus, there is no need for a 100 % control of each vial of a batch. Due to the fact that during the initial freezing process the (non-sterile) liquid nitrogen is not in direct contact with the sprayed pharmaceutical formulation, the manufactured nanocomposite pellets can be used as an instant water-soluble product for sterile injections. In this context, the containment technology used for the whole process in a laboratory and in an industrial environment (see Fig. 2.4.1 and Fig.2.4.2) is of primary importance to being approved by FDA. Thus, nanocomposite medical pellets can serve as a societal blessing in contrast to the harmful diesel exhaust. Unfortunately, diesel exhaust does not only contain micro particles of the diesel exhaust scandal, but also a substantial amount of nanoparticles, which is not subject to existing regulations.

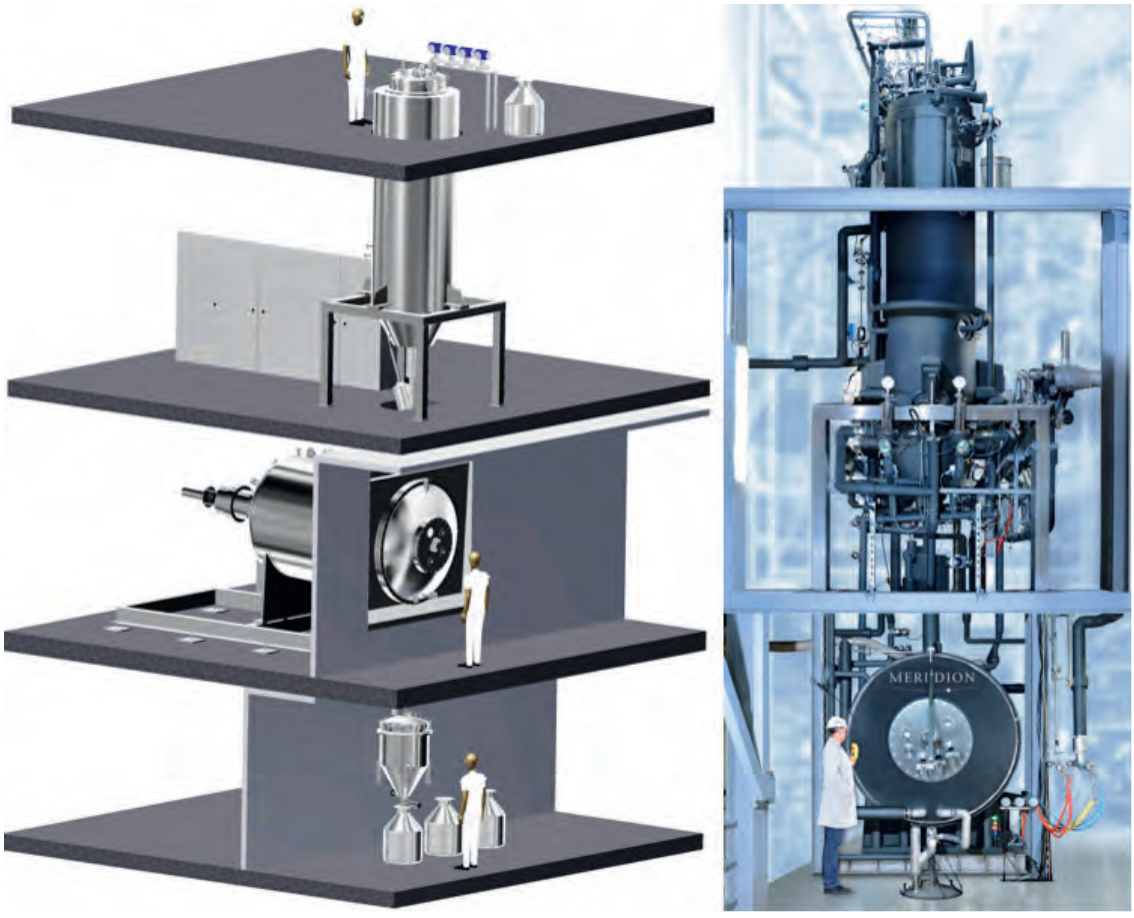

Fig.2.4.2: Industrial Spray Freeze-drying Concept for Aseptic (full containment) Processing. (Courtesy Meridion).

3. Spray freeze-drying as a safe Technology Platform for the Production of Nanoparticles

3.1. Range of Applications in the Pharmaceutical Industry and beyond

Most of the novel highly potent drugs developed on the basis of modern molecular medicine, taking into account cell surface recognition techniques for precision medicine, show poor water-solubility. A chemical modification of the drug substance enhancing the solubility often decreases the pharmacological activity. Hence, as an alternative, increase of the solubility can be obtained by the formulation of micro or nano sized drug particles. Unfortunately, nanosized particles are often not physically stable and need to be stabilized in an appropriate matrix. Thus, it is important to manufacture nanostructured, composite systems which can be efficiently realized by the innovative spray freeze-drying process with a broad range of applications.
This platform allows the manufacturing of stable formulations of vaccines, which need not to be kept at –77°C for long term storage as in case of Pfizer/BioNTech or at –20°C for the Moderna vaccine manufactured by Lonza. Both vaccines are manufactured based on mRNA technology, respectively, using mRNA encapsulated in lipid nanoparticles (Fig. 3.1).

Fig. 3.1 shows that the messenger RNA is picked up by the cell, staying in the cytosol of the cell, without entering the nucleus of the cell. Thus, the mRNA vaccine is not able to alter the DNA of the nucleus, a widespread disinformation in social media *(RNA vaccine – Wikipedia)*. It is important to notice that the RNA vaccines offer advantages for the following reasons: a) the manufacturing process is cheaper; b) is faster; c) is better standardized, and, last but not least, is not based on attenuated (weakened) or killed forms of the pathogenic virus. Thus, the manufacturing process of the traditional vaccine needs to be safe to avoid inacceptable side effects.

New research findings show that the health condition of the human being depends, among other factors, on the quality and composition of the intestinal microbiome **(Leuenberger H, 2019 a).** Indeed, the positive role of **friendly** microorganisms **(bacteria)** in

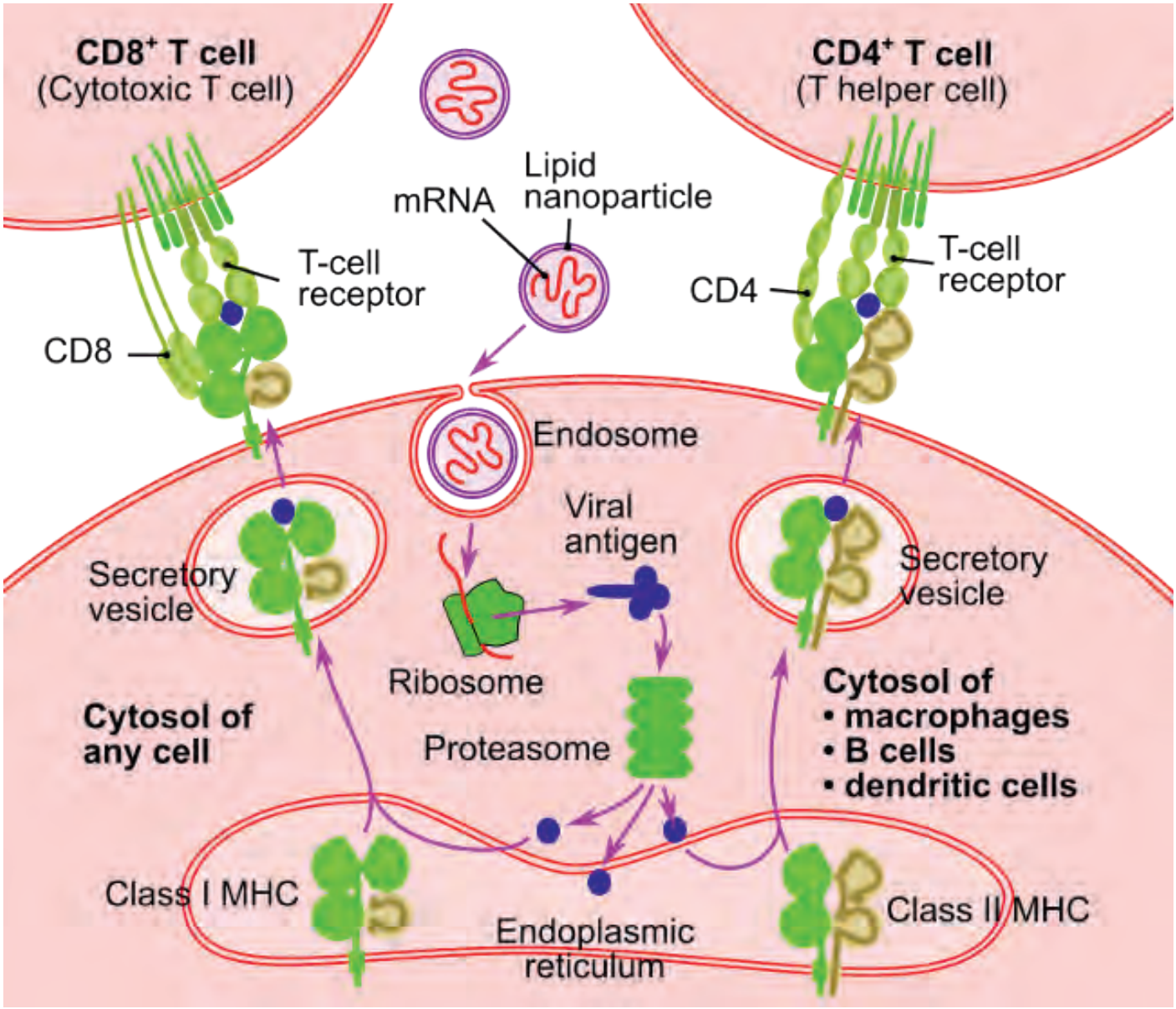

Fig. 3.1: The mRNA (messenger RNA) technology uses lipid nanoparticles as delivery vector for manufacturing the vaccine, inducing the immune response. According to Bernhard Luy (MERIDION), both mRNA molecules (Qiu et al, 2019) and lipid nanoparticles have been described in the literature to have successfully undergone lyophilization; therefore spray freeze drying can be considered as a promising option for appropriate mRNA formulations. (Courtesy RNA vaccine, Wikimedia Commons).

our intestine is now in the focus. In this context, **the contemporary research needs, also, to embrace the friendly types of viruses!**

This **is an urgent request** since we can take advantage of **Bacteriophages (= viruses)** to clean up our waste water **(Withey S et al, 2005)** and we can use **phage therapy** (Wikipedia) for an effective and optimal treatment of antibiotic resistant bacteria. In addition, as mentioned in the ppt presentation at the Nano Science & Technology symposium at Fukuoka (Japan) in 2017, **the phage therapy could in principle also be used** for **curing cancer patients (Leuenberger H, 2017).** It has to be emphasized that the patients **are cured** and not simply treated based on classical chemotherapy with side effects and with the uncertainty that the cancer therapy is successful. The phage therapy or therapy **of cancer patients with a friendly** virus is based on the following concept: The phage (virus) is looking for the human specific cancer cell as a host for its replication. It is important to realize that **only the malign cancer cells serve as host cells,** which explains that **this treatment is a cure without side effects.** The other very positive point is the following: The **MERIDION spray freeze technology is the process of choice for a safe, efficient and aseptic production of such a high-precision medicine.** The active ingredients, the phages, have the size of nanoparticles (Fig. 3.2) which need to be delivered to the cancer cell or to the pathogenic bacteria being resistant to antibiotics (Fig. 3.3).
It remains the hope that enough funds will be available, like in the case of finding a COVID vaccine, to explore new research avenues for the advancement of nano science and technology in the area of phage therapy. In addition to these advanced therapies for treating patients, the MERIDION technology can be successfully used for the aseptic production of formulations of classical high potent, thermo-sensitive, poor water-soluble drugs, of vaccines, biosimilars, biologics, monoclonal antibodies, and antibody-drug conjugates for precision-medicine.

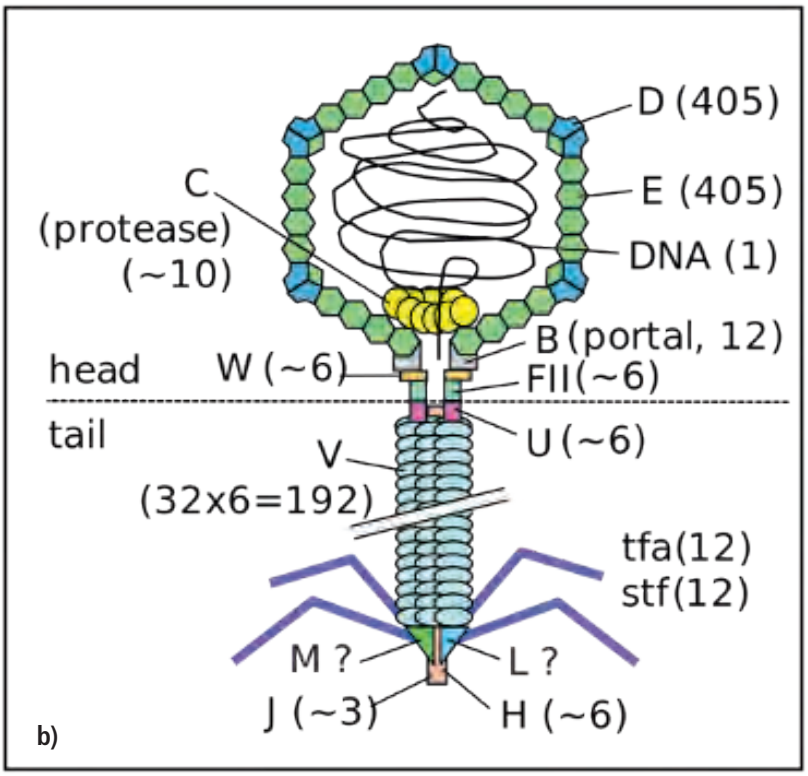

Fig. 3.2 a/b: Scheme of the Lambda phage [a] with the capsid (typical diameter 20 nm) on the top. The DNA [b] is used to replicate the virus in the host cell, such as a pathogen bacteria or a cancer cell. (Courtesy Wikimedia Commons).

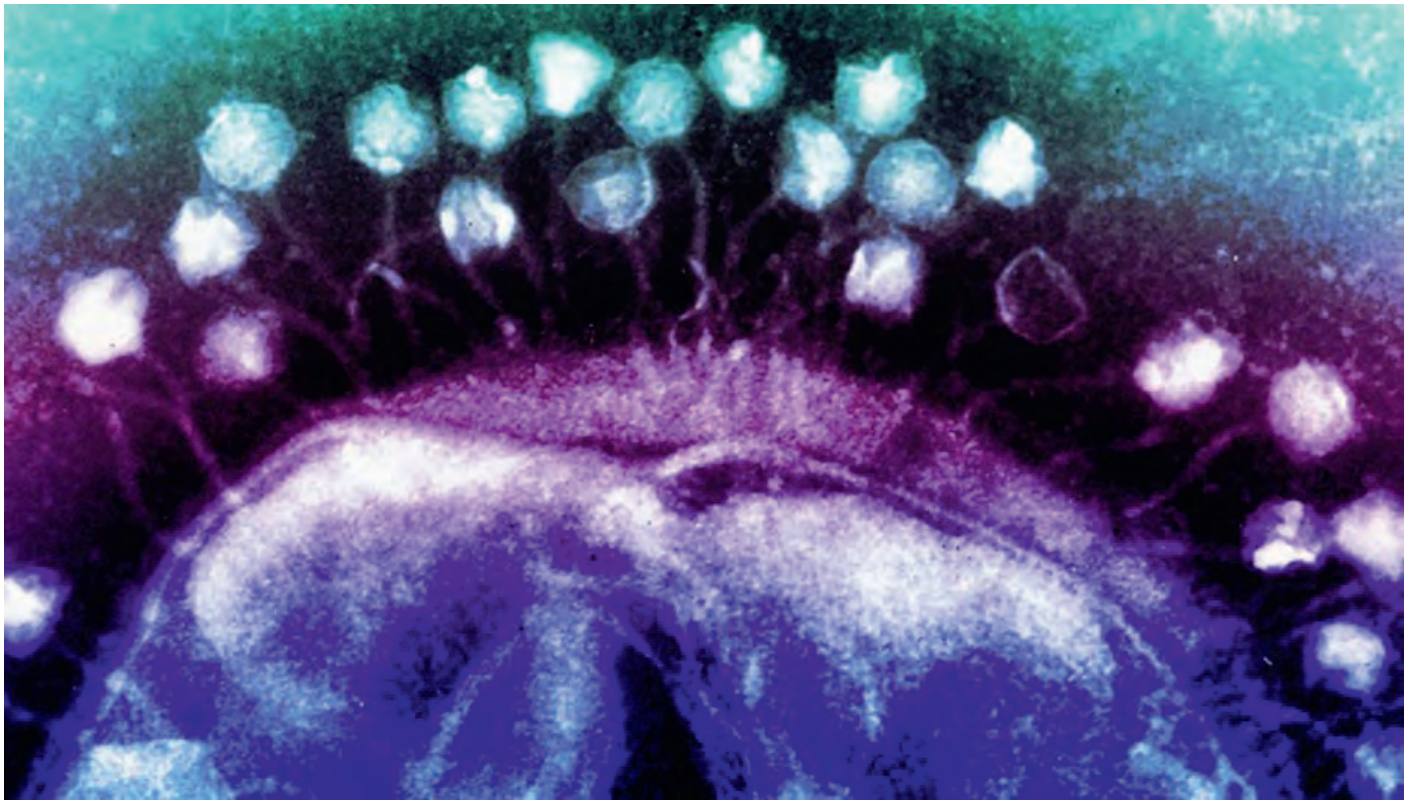

Fig.3.3: Cell (resistant to antibiotic treatment, or a cancer cell) being attacked by «friendly» phages using the cells as «food» and as hosts for replication of the viruses, respectively. The «friendly» virus in the human body is only active as long as there is «food» for its replication.

Due to the problem that natural phages cannot be patented, the incentive to do research by the pharmaceutical industry slowed down, but there is an opportunity that engineered and optimized phages can **(Glasgow J & Tulllman-Ercec D, 2014)** be patented. The latter point is not discussed in the following article «Business Ethics in the Pharmaceutical Industry and Beyond» in this issue SWISS PHARMA issue 43 (2021) No. 4.

Due to the fact that the spray freeze-drying of poor water-soluble, high potency drugs is approved as a **standard operation procedure** by the FDA **(Guidance for industry, 2006),** this platform technology should be used for manufacturing clinical samples for clinical phase I studies for all types of drugs.
Thanks to this platform the FDA concept of «Right, First Time» could be rigorously interpreted **(Leuenberger H, Leuenberger MN. Puchkov M, 2010)** already, in an early phase of the development of novel drugs **(Leuenberger H, Puchkov M, Schneider B, 2013).**

This concept is a prerequisite that an optimal quality of the final marketed drug dosage form used in clinical phase III can be achieved **(Leuenberger H and Leuenberger M N, 2016).** Accordingly, failures as a result of poor drug water-solubility can be avoided for clinical phase I studies. The rigorous implementation of the concept «Right, First Time» in combination with this innovative platform and the implementation of the in-silico design of solid dosage forms will allow the pharmaceutical industry to adopt the successful workflow of the automotive and aircraft industry **(Maneerojpakdee, D et al, 2017).**

This workflow was successfully introduced by Go Kimura at the company Shionogi in Japan. In addition, the current failure rates of the clinical phase I-III studies can be substantially reduced by using the above concepts. Johannes von Orelli **(Von Orelli J, 2005)** demonstrated with his PhD thesis the problem of capsule formulations with a poor wettability, if a higher strength of drug dosage is needed without compromising the bioavailability of the capsule formulation for clinical phase I studies.

It is important to notice that the MERIDION spray freeze-drying technology for manufacturing tailor made nanoparticles is used in high-tech 3D sound devices of the consumer electronics industry **(Leuenberger H, 2017, 2019b).** In this case multiple drying units allow a continuous 24h/7d manufacturing process.

4. Conclusions

The spray freeze-drying process is used for the safe manufacturing and handling of nanocomposite pharmaceutical products. The technological prerequisites can be summarized as follows:

- The manufacturing process of this platform follows in detail the same technological prerequisites as other pharmaceutical products to grant safety.
- As a result, the manufacturing process follows the needs of the regulations of the health authorities such as FDA and EMA.
- In this context, the containment concept and the concept of aseptic processing play an important role.

The results of this conclusion prompt the following important questions:

- Do we agree that the same regulations should be applied for all manufacturing processes regarding nanoparticles beyond the pharmaceutical industry?
- Is it necessary to adopt a broader view to protect the interests of the patient and the consumer?

Both points are discussed in the following contribution: Business ethics and Nanoparticles in this SWISS PHARMA 21/4 issue.

5. Acknowledgements

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