Technical Note – N°. 906/2025

Essential solutions for chemistry R&D workflow

Abstract: This document presents an optimized Chemistry R&D workflow using BUCHI's essential instruments: Rotavapor® R-80/R-180 for solvent evaporation, Pure Essential for flash chromatography, and Lyovapor™ L-210/L-250 for freeze-drying. The system integration enables safe and efficient sample handling and helps conserve bench space.

1. Introduction

In a standard Chemistry R&D laboratory workflow, the synthesized mixture is initially concentrated by reducing the solvent volume, typically through rotary evaporation. The resulting crude extract is then subjected to purification, beginning with flash chromatography for rapid compound separation. When higher resolution is necessary, preparative HPLC is employed. Fractions containing the desired compound are identified, collected, and combined.

Following chromatographic separation, the target compounds are often present in dilute solutions and require further concentration before downstream processing. To remove residual solvents, particularly from heat-sensitive substances, freeze-drying (lyophilization) is commonly used. This step helps to prevent thermal degradation and maintains the integrity of the compounds.

The following sections explain how to select and operate BUCHI's most essential instruments and accessories to ensure optimal performance throughout each stage of the workflow. These include the Rotavapor® R-80 and R-180 for solvent evaporation, the Pure Essential for flash chromatography, and the Lyovapor™ L-210 and L-250 systems for freeze-drying.

2. General Procedure on Rotavapor® R-80 and R-180

Rotary evaporation is a widely used technique for the efficient removal of volatile solvents under reduced pressure. Although often considered a routine process, adhering to proper procedures is important to ensure safe and efficient operation. The Rotavapor® R-80 and R-180 combine a compact footprint, intuitive operation and high-quality materials to ensure gentle, efficient, and reproducible solvent removal.

2.1 Rotavapor® Configurations

The Rotavapor® R-80 accommodates flasks up to 1 L, while the R-180 supports a maximum flask size of 3 L. Both models are available either as standalone units or integrated into a complete BUCHI evaporation system.

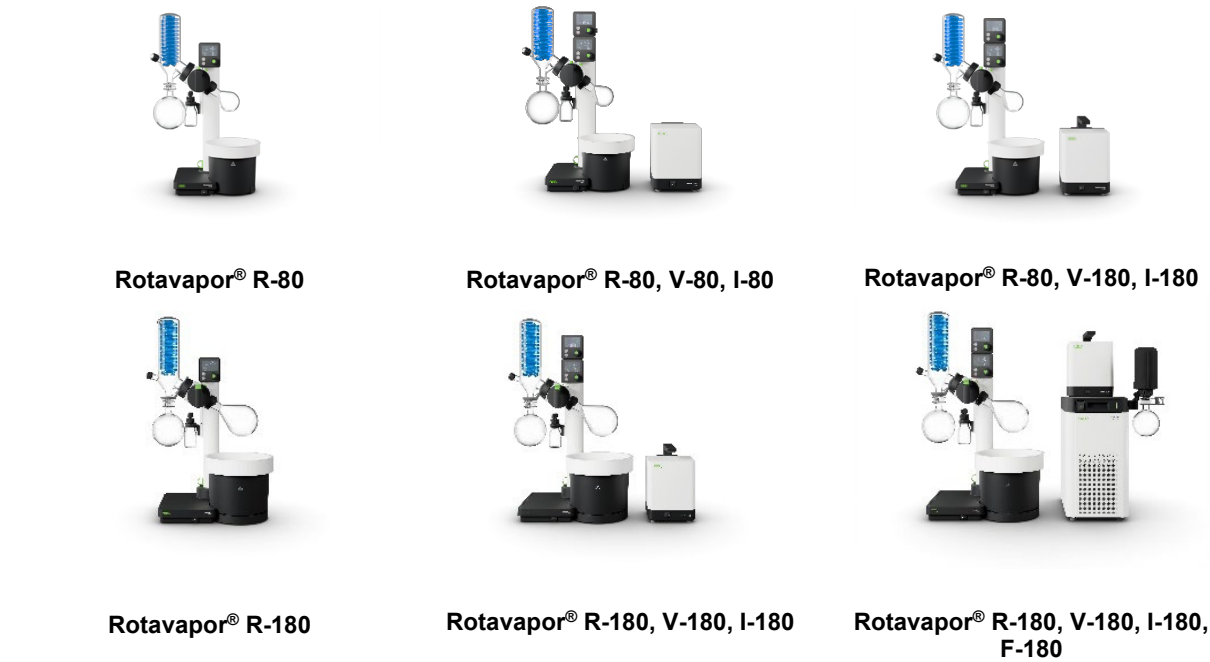

Figure 1: Configurations for Rotavapor® R-80 and R-180.

For vacuum generation, the Vacuum Pump V-180 (1.5 m³/h, 10 mbar ultimate pressure) is operated via the Interface I-180, which allows for precise vacuum control using predefined pressure settings. For applications with simpler requirements, the Vacuum Pump V-80 (1.3 m³/h, 15 mbar ultimate pressure) can be used in combination with the Interface I-80, enabling manual vacuum regulation through adjustable pump speed and fine-tuning via a needle valve. Both pumps feature speed-controlled operation for improved performance and energy efficiency. To support cooling, the Recirculating Chiller F-180 (550 W cooling capacity at 15 °C, operating range 0 °C to ambient) is capable of supplying temperature control for up to two Rotavapor® units simultaneously.

2.2 System Preparation

Before starting a distillation, it is important to ensure that all system components are properly connected and that the setup is airtight. The Leak Test function available on the Interface I-180 provides a convenient and reliable method for verifying the system's integrity prior to operation.

The heating bath should be filled with water. When using pure distilled or deionized water, it is recommended to add approximately 1 g of borax ($Na_2B_4O_7 \cdot 10H_2O$) per liter to inhibit corrosion. Alternatively, tap water may be blended with distilled water at a ratio of up to 1:1, depending on the local water hardness.

2.3 Evaporating Flask Selection

The size of the evaporation flask has a significant influence on process efficiency. Larger flasks provide greater surface area, which enhances solvent evaporation and helps minimize bumping. For example, increasing the flask volume from 250 mL to 1 L can result in a 2.5- to 3-fold increase in evaporation rate.

To maximize performance, the evaporation flask should be immersed as deeply as possible in the heating bath, ensuring optimal heat transfer.

When working with powders, the use of beaker flasks with wide openings is recommended. These offer several practical benefits:

- Easier removal of product.
- Reduced transfer time.
- Simplified cleaning.

The evaporation flask should always be attached with a firm but gentle grip to avoid stress on the glassware. Over-tightening can lead to breakage. The Combi-Clip (Figure 2) supports safe and efficient handling by:

- Securely holding the flask in place.
- Aiding in the release of stuck flasks.
- Enabling easy removal of the vapor duct.

Figure 2: Combi-Clip for easy flask handling.

2.4 Start-Up Procedure

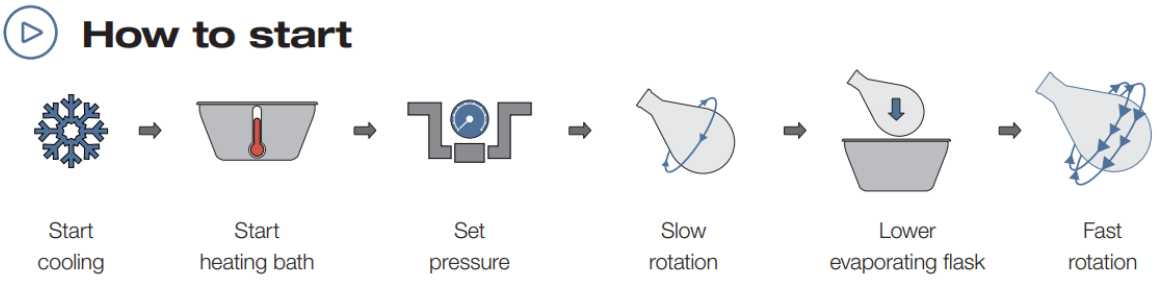

Figure 3: The recommended starting procedure on a rotary evaporator.

Once the system is fully assembled, follow the start-up procedure as illustrated in Figure 3. Begin by activating the chiller and heating bath, which can be controlled directly via the Rotavapor® display. This ensures that both temperature regulation systems are stabilized before initiating the evaporation process.

2.5 Delta 20 Rule

It is important to match the chiller's cooling power and the heating bath's heating capacity to the process requirements. A practical guideline is the Delta 20 Rule, which suggests maintaining a 20 °C difference between the cooling medium and the boiling temperature, as well as between the boiling temperature and the heating bath.

For example, if the chemical product must not be heated above 24 °C, distillation at 24 °C requires a cooling medium temperature of 4 °C or lower and a heating bath temperature of 44 °C. The optimal parameters are therefore 4 / 24 / 44 °C.
For the distillation of diethyl ether at atmospheric pressure, which has a boiling point of 35 °C, the cooling medium temperature should be 15 °C or lower, while the heating bath temperature should be 55 °C. Thus, the optimal settings are 15 / 35 / 55 °C.

2.6 Pull Vacuum

With everything in place, it's time to pull the vacuum. One common mistake is reducing the pressure too quickly. Dropping straight down to 10 mbar often results in foaming and bumping. A gradual decrease allows your sample to adjust smoothly.

Select the working pressure by looking up the recommended values in a solvent table. Once the optimal pressure is reached, maintain it steadily. Sudden pressure fluctuations can disrupt the distillation process or cause bumping. Using the speed-controlled Vacuum Pump V-80/V-180 helps ensure stable vacuum conditions and minimizes bumping risks.

2.7 Rotation Speed

Start with a low rotation speed when lowering the flask into the water bath to prevent splashing and avoid contact with hot liquid. Once the flask is fully immersed, you can safely increase the rotation speed.

Key points to consider:

- Optimal rotation speed depends on sample and flask size.
- Increasing speed generally enhances turbulence, improving heat transfer and evaporation efficiency.
- Excessive speed can reduce turbulence by pressing the sample against the flask walls.
- For 1 L flasks, a rotation speed of 250–300 rpm is ideal.
- Lower speeds are recommended for drying or when working with high-viscosity samples.

2.8 Monitor Condensation

Once evaporation begins, closely monitor the condensation on the condenser. Ideally, about 75% of the condenser length should be covered with visible condensation. If the condensation level is too high, it suggests that vapors are escaping due to a coolant temperature that is too warm or a vacuum that is too

strong. On the contrary, if the condensation level is too low, the vacuum is insufficient, causing the evaporation process to proceed more slowly than necessary. Maintaining the proper condensation level is essential for efficient and controlled evaporation.

2.9 Stopping Process

To stop the process, follow the procedure outlined in Figure 4.

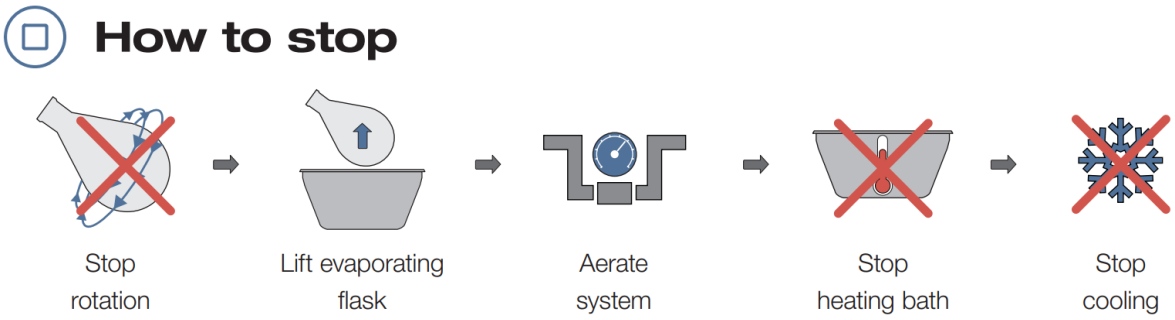

Figure 4: The recommended stopping procedure on a rotary evaporator.

2.10 Space Saving

The Rotavapor® R-80 has the smallest footprint among rotary evaporators currently available, making it suitable for use in limited spaces such as crowded lab benches or fume hoods. The compact heating bath for maximum flask size of 1 L uses up to 40% less energy compared to standard larger-volume baths.

Both the Rotavapor® R-80 and R-180 have a rotatable interface (Figure 5) that allows angled positioning to accommodate busy lab benches and fume hoods while maintaining direct access to all control elements.

Figure 5: Rotatable interface on the Rotavapor® R-80 to allow angled positioning on crowded lab benches.

3. General Procedure on Pure Essential

Flash chromatography is a highly effective technique for separating complex samples, such as synthesized mixtures or biological crude extracts, into their individual components for preparative applications. It offers the resolution and flexibility required to efficiently isolate target compounds, even from challenging sample matrices. The Pure Essential system enhances purification workflows by automating key steps and significantly reducing manual intervention, thereby improving both efficiency and reproducibility.

3.1 Pure Essential Configurations

Pure Essential features a modular design centered around the Pure C-900 pump with integrated controller, which significantly enhances separation speed and improves reproducibility. To further increase efficiency, the system can be seamlessly expanded with the Pure C-106 fraction collector and the Pure C-107 UV detector.

Adding the fraction collector enables unattended operation and volume-triggered collection, allowing for streamlined workflows. The UV detector provides real-time monitoring of the separation process, enabling precise peak collection. This reduces the volume of solvent that needs to be evaporated and eliminates the need for time-consuming TLC analysis.

When combined, the pump, fraction collector, and UV detector deliver the full benefits of automated flash chromatography-maximizing efficiency, accuracy, and time savings.

Pure C-900

Pure C-900 + Fraction Collector C-106

Pure C-900 + UV Detector C-107

Pure Essential: Pure C-900 + Fraction Collector C-107 UV Detector C-106

Figure 6: Configurations of Pure Essential.

3.2 Solvent Lines & Priming

To begin the purification process, the Pure C-900 pump must be connected to the appropriate solvents used for separation. The system supports the simultaneous use of up to two solvents (A and B), which can optionally be placed on a dedicated solvent platform located on top of the instrument for convenience and space efficiency.

Solvent bottle caps are designed to support clear labeling, provide secure connections for solvent lines, and are compatible with carbon filters to improve solvent purity. Additionally, solvent filters can be optionally attached to the ends of the solvent tubing to prevent particulate contamination.

Once the solvent lines are defined and connected, the system should be primed for the following reasons:

- To remove air from the system (Common causes of air bubbles include: an unsecured cartridge holder, loose ferrules on solvent lines, incorrect loop connections, or non-degassed aqueous solvents.).
- To verify that the correct solvents are filled and available for the separation process.
- To identify potential leaks before starting a run.
- To clear any blockages in the solvent path.

Each priming cycle consumes approximately 50 mL of solvent per line.

3.3 Connection of Flash Cartridges and Glass Columns

Pure Essential enables the connection of flash cartridges and glass columns. Depending on their size, these consumables can be attached via an optional cartridge holder and a clamp directly to the instrument or connected via an external holder.

Table 1: Overview of connection possibilities of flash cartridges and glass columns on Pure Essential.

Flash cartridges	Glass columns
4–330 g: via optional cartridge holder and Pure clamp	ID 15/26 mm: via optional cartridge holder and Pure clamp
>330 g: external V-stand	ID >26 mm: external V-stand

Figure 7: Pure Essential connected with a flash cartridge (left) and glass columns of different sizes (right).

Pure Essential allows the user to work either with gravity or anti-gravity flow. Anti-gravity flow through the cartridge reduces dead volume and allows for easy air bubble removal.

Note: For the connection of flash cartridges with a luer lock outlet, use a Luer Adapter 1/4-28 Male.

3.4 Equilibration

Before injecting the sample, the silica of the flash cartridge or in the glass column has to be equilibrated. The equilibration of flash cartridges or glass columns facilitates a uniform and steady flow of sample and solvent by removing any trapped air during the separation process. This helps to avoid undesired separation issues, such as unresolved compounds and low purity fractions. Besides that, it helps to stabilize system pressure, especially important in automated systems and it also allows early detection of any issues like blockages or leaks. Typically, a column or cartridge is equilibrated by flushing it with 5–10 column volumes (CV) of the starting solvent.

3.5 Sample Injection

Pure Essential supports various injection modes to match specific solid and liquid loading applications. Liquid loading can be done directly on the cartridge, into a loop or chamber mounted on the Pure cartridge stand and connected with the flash cartridge. Besides that, solid samples can be connected via the cartridge stand using the Pure clamp.

It is generally advised to follow the loading capacities of the flash cartridge as overloading decreases efficiency. The ideal sample volume should not be more than 10% of the column volume (CV). The more retentive the sample is, the more volume can be loaded.

3.6 Liquid injection

Pure Essential provides different ways to load liquid samples on the flash cartridge:

- Directly on the cartridge:
  Liquid samples can be injected directly into the cartridge with the help of an optional T-piece and injection valve. The injection is done after the equilibration of the flash cartridge. Both items can be left on the cartridge while equilibration.

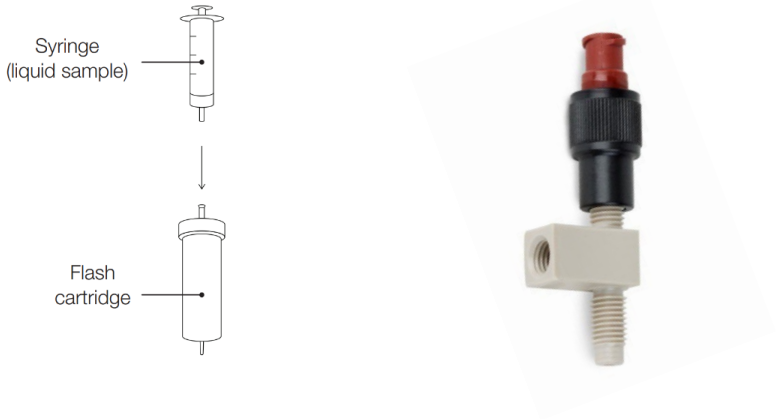

Figure 8: Injection of a liquid sample into a flash cartridge using a T-piece (right).

- Via an injection unit and a loop:
  Use the Injection Unit (6-way valve) for safe and efficient sample loading. This optional valve is mounted on the optional cartridge stand and connected to the sample loop (made of ETFE; sizes 5 mL or 20 mL). First equilibrate your cartridge in the “Load” position. Then switch to “Inject” position and introduce the sample using a syringe at the designated port on the injection unit allowing it to fill the loop. Switch manually back to the “Load” position to start the run.

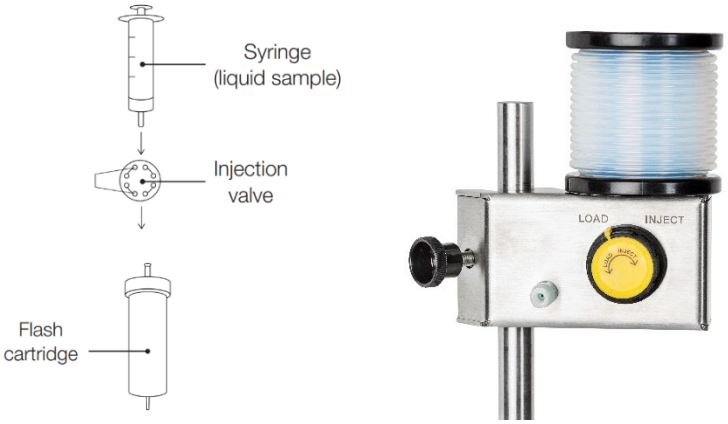

Figure 9: Injection of a liquid sample into a flash cartridge via a loop mounted on an injection unit (right).

- Use the Injection Unit (6-way valve) for safe and efficient sample loading.
  This optional valve is mounted on the optional cartridge holder and connected to the sample chamber (made of glass; sizes 100 mL, 250 mL, 500 mL and 1000 mL). First equilibrate your cartridge in the “Load” position. Load your sample with a funnel into the chamber and switch to “Inject” position. Open the gas valve and inject your sample from the chamber into the cartridge. Stop the injection before gas enters the tubing to the cartridge by switching to the “Load” position and start the run.

To maximize sample recovery, flush the sample loop or chamber with some solvent after injection in the “Load” position.

3.7 Solid Loading

Pure Essential allows you to apply a sample to the flash cartridge in a dry or pre-adsorbed form using a solid loader. The preparation of a solid sample is as follows:

- The crude sample is dissolved in a suitable polar solvent.
- This mixture is then incubated for a few minutes in an ultrasonic bath to enhance the solubility.
- The mixture is filtered to get rid of material that has not fully dissolved.
- Silica is added to the mixture at 5 times the weight of the crude sample.
- The solvent is removed completely by using a Rotavapor®.

Figure 10: Rotavapor® R-80.

Finally, the solid sample, which now consists of a mixture of crude sample and silica, is packed into the Pure solid loader (15 g or 40 g size), which is then fitted via a solid loader connection kit with the Pure clamp on the cartridge stand in front of the separation cartridge into the solvent flow.

Figure 11: Injection of a solid sample into a flash cartridge via a solid loader (right).

After equilibration of your cartridge, connect your solid loader with the inlet of your cartridge and start the run. The fluidic path will go through the solid loader and inject the sample into the flash cartridge.

3.8 UV Detection

Pure Essential offers a modular design, centered around the Pure C-900 pump. To further boost efficiency, the system can be expanded at any time with the addition of the Pure C-107 UV detector, which eliminates the need for TLC analysis, saving more time.

Four fixed wavelengths can be chosen: 254 nm, 275 nm, 325 nm and 365 nm. It can be easily installed at the rear of the pump, is therefore easily accessible and serviceable.

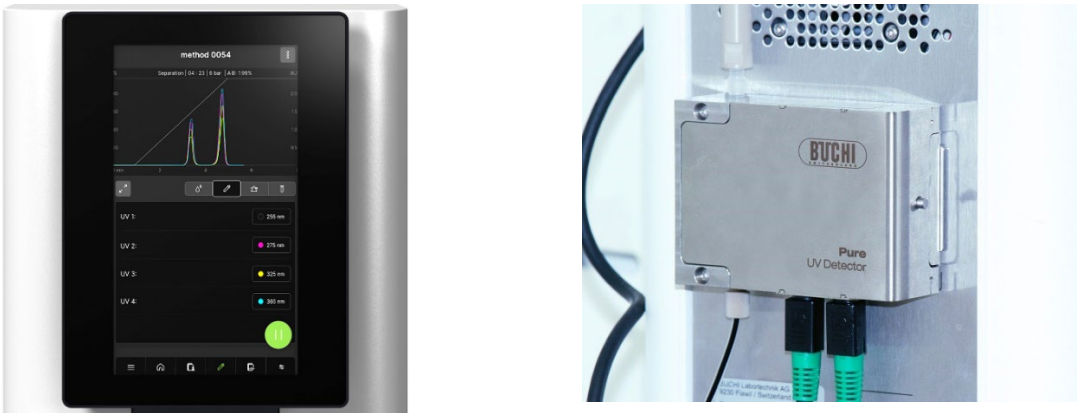

Figure 12: The software screen of the Pure Essential displays four fixed UV wavelength options (left). The Pure C-107 UV detector is mounted on the rear of the Pure Essential Pump C-900.

3.9 Fraction Collection

The Pure C-106 fraction collector stands out for its exceptional flexibility and safety features. It offers the largest fraction collector bay on the market, complete with internal illumination for easy observation of sample collection. A switchable lamp enhances visibility as needed. Key features include:

Low-dead-volume collection valve positioned directly at the nozzle.
Illuminated and spacious collection bay for convenient monitoring and handling.
Fraction collector needle position gets continuously and automatically recalibrated.

- Various safety features protect the user as well as the sample: closed and active ventilation, excess solvent overflow system (can hold 1.4 L of spilled solvent), excess sample is contained after the sample loop in a vial.

The fraction collector is compatible with various racks, such as:

- Competition racks are either programmed in the software by default or can be programmed in the software. These racks cannot automatically be chosen by the software, as the RFID tags cannot be read.
- Customizable racks will be able to be programmed in the software. As long as the racks fit in the fraction collector bay, any position can be filled.

Pure Essential enables direct collection into Rotavapor® flasks, simplifying transfer to the BUCHI Rotavapor® and Lyovapor™ system. Other special racks allow to collect into funnel racks and jars. Additionally, BUCHI racks, including the vials, can be conveniently cleaned in a dishwasher using the appropriate accessory.

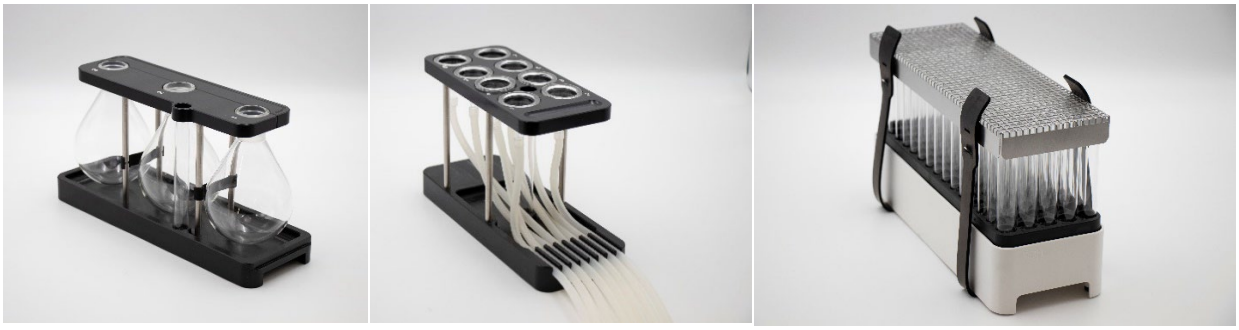

Figure 13: Pure racks for collection into evaporation/ freeze-drying flasks, funnels and with a dishwasher accessory.

3.10 Space Saving

The Pure Essential boasts the smallest footprint on the market. Its modular design allows users to choose their setup: either save space by placing the pump on top of the fraction collector or position it beside the instrument, freeing up room for solvent bottles above the collector. The instrument even allows to stack pumps or fraction collectors.

Figure 14: Stacking options with Pure Essential.

4. General Procedure on Lyovapor™ L-210/L-250

Freeze-drying, or lyophilization, is a gentle dehydration process widely used to preserve the stability and activity of heat-sensitive compounds. By removing the solvent through sublimation under vacuum, it ensures minimal degradation and extends the shelf life of products. The BUCHI Lyovapor™ L-210 and L-250 freeze-dryers offer reliable performance with flexible chamber sizes to suit different sample volumes.

4.1 Evaluating Solvent Suitability for Freeze-Drying

Many aqueous samples can be freeze-dried with ease, as water is typically fully collected on the condenser during most processes. However, organic solvents present additional challenges due to their often low freezing points, which can be well below the condenser surface temperature.

To determine whether a solvent is suitable for freeze-drying, four key factors must be evaluated using the solvent's vapor-pressure curve:

- Freezing capability: Which method can achieve sufficiently low temperatures to fully freeze the sample?
- Freezing concentration: Does the solvent require dilution to freeze effectively?
- Condenser efficiency: Is the condenser temperature at least 15–20 °C lower than the solvent's freezing point to ensure collection?
- Sample phase stability: Can pressure be maintained low enough to keep the sample frozen throughout the process?

Key considerations include:

1. Organic solvents often require dilution with water or the use of liquid nitrogen to reach freezing temperatures.
2. Many organic solvents have freezing points too low for even -85 °C or -105 °C condensers to trap effectively, limiting vapor collection differences between -55 °C and colder condensers.
3. If the solvent is not trapped by the condenser, it will pass through the system as vapor via the vacuum pump.
4. Due to low freezing points and triple points, it may be difficult to evacuate the chamber quickly enough or maintain sufficiently low pressure to prevent melting, even at ultimate vacuum.
5. Diluted solutions may exhibit solvent melting and evaporation while water remains frozen (indicated as yellow zones in solvent tables), which may or may not affect sample quality depending on requirements.
6. Excessive solvent volumes can prevent maintaining required vacuum pressure, causing the sample to melt and evaporate (red zones in solvent tables), necessitating process termination.

4.2 Lyovapor™ Configurations

Following aspects are important to choose the right freeze-drying configuration for your application:

- If possible, eliminate as much of the solvent in your sample as possible prior to freeze-drying using a rotary evaporator for example R-80.
- Choosing the right pump is crucial when solvent vapors are leaving the system. A scroll pump (Edwards scroll pumps nXds 6iC) is recommended for all freeze-drying applications involving solvent in large quantity. Make sure that the exhaust port of the pump sits in a fume hood to avoid any human exposure to the solvent.

The Lyovapor™ L-210 and L-250 offer fully automated, continuous sublimation with precise control of process parameters, ensuring reliable and reproducible freeze-drying results.

The following lists give a review of solvents often used in combination with water and show whether or not they can be removed by freeze-drying on Lyovapor™ L-210 and L-250.

	The sample can be freeze-dried properly. Sublimation occurs.
	The pressure in the drying chamber cannot be set to a low enough value to maintain the solvent on solid form. The solvent will melt while water will remain in ice form. The solvent will evaporate and an increase in pressure can be observed until it is completely evaporated. The ice will then sublimate. Even though the solvent is not sublimating, evaporating is good enough for many applications.
	Not working – not possible.

Table 2: Color descriptions for the solvents.

Lyovapor™ L-210

Solvent	Concentration %
Water	100
DMSO	100
Acetic acid	≤ 5
Trifluoroacetic acid	≤ 5
Acetonitrile	≤ 5

Figure 15: Solvent list (left) for Lyovapor™ L-210 (right).

Lyovapor™ L-250

Solvent	100%	60%	30%	10%	≤ 5%
Acetic acid					
Acetone					
Acetonitrile					
Dimethyl sulfoxide					
Ethanol					
Isopropanol					
Methanol					
Trifluoroacetic acid					
tert-Butanol					
Formic acid					
Dimethylformamide					
Dioxane					

Figure 16: Solvent list (left) for Lyovapor™ L-250 (right).

4.3 Sample Quantity

In typical freeze-drying operations, instruments often handle multiple samples with varying solvent volumes, compositions, and surface areas. This diversity requires adequate condensing capacity in the ice condenser to efficiently capture vapor released from sublimating samples in flasks, trays, and other containers. To meet these demands, Lyovapor™ offers three ice condenser capacities–4 kg, 6 kg per 24 hours–ensuring the system is always prepared for high sample throughput and optimized drying efficiency. These units achieve solvent recovery rates of 95–99%, enabling safe and reliable drying at condenser temperatures of –55 °C and –85 °C.

4.4 Containers

The surface area created during the freezing step has a significant impact on freeze-drying time. Freeze-drying progresses from the top down, forming a dry layer over the remaining frozen product. As this layer thickens, it becomes increasingly difficult for water vapor to escape, slowing the process.

To optimize drying efficiency, it's important to maximize the sample's surface area. This starts with selecting the appropriate container size and type BUCHI offers a wide range of beaker and round flasks in various sizes, as well as trays suitable for both liquid and solid samples.

Figure 17: Lyovapor™ sample container for manifold drying chamber.

For round-bottom flasks, liquid samples can be frozen under rotation in a cooling bath containing dry ice or liquid nitrogen. The rotation distributes the sample evenly along the inner wall of the flask, forming thin layers approximately 2 cm thick, depending on the sample volume and flask size. This method significantly increases the available sublimation surface, reducing freeze-drying time by up to 50% compared to samples frozen statically in a conventional freezer.

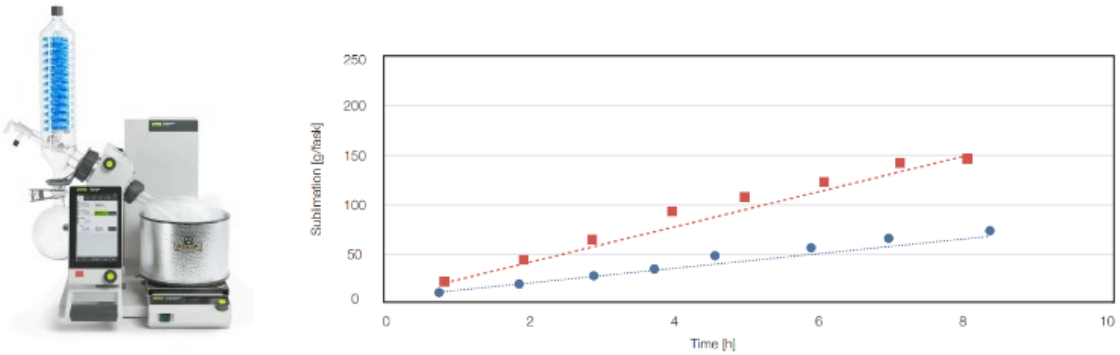

Figure 18: Shell (rotational) freezing using a Rotavapor® R-300 and the Dewar accessory (left). Sublimation in g/flask with (red square) and without (blue dots) rotational freezing (right).

4.5 Vacuum and Temperature Setting

Freeze-drying without a defined pressure setting—also known as drying at low pressure—is the simplest approach. Anyhow, setting and precisely maintaining pressure leads to significantly shorter drying times and more reproducible, reliable results.

- Pressure control is key to efficient sublimation:
  - Sublimation is driven by heat transfer via convection and the pressure difference between the ice surface in the condenser and the frozen sample.
  - Increasing the set pressure from 0.2 to 1 mbar can enhance sublimation by approximately 5%.

- Advanced vacuum control for precision and reproducibility:
  - BUCHI Lyovapor™ systems feature a combination of main, control, and aeration valves.
  - This enables precise vacuum control with a deviation of only ±5% within the range of 1 to 0.03 mbar.
  - The result is maximized process consistency and repeatability.

- Boosting performance with heatable shelves:
  - Sublimation requires energy input; for samples placed on a shelf, heat is transferred by conduction.
  - Increasing heat input accelerates drying, but it must be balanced with the sample's critical temperature to avoid product damage.

- Controlled heating for safe and efficient drying:
  - Heatable shelves are the most common accessory for supplying thermal energy.
  - Shelf temperatures are automatically adjusted according to the programmed method.
  - In combination with a sample temperature probe, the impact of heating can be tracked in real time.
  - These temperature data are essential for developing an optimized freeze-drying program with the ideal pressure and shelf temperature settings, ensuring fast drying and preventing sample collapse.

Figure 19: Heating shelf for continuous thermal energy supply and connection to sample temperature tracking.

4.6 Endpoint Determination

Of the three phases in a freeze-drying process, primary drying is by far the longest. Optimizing this step can yield significant time savings and improve overall process efficiency. Reducing the duration of primary drying, while also ensuring it is not ended prematurely, is critical for maintaining product quality.

Ending primary drying too early, before all ice has been removed, can lead to serious product defects such as collapse or eutectic melt. Several factors influence the duration of this phase:

- Sample concentration.
- Sample volume and size.
- Type and geometry of the sample container.

Primary drying time can also vary from batch to batch, even under the same general conditions. Because of this variability, having an automated method for detecting the endpoint of primary drying would offer both economic and quality advantages.

4.7 Pressure difference test

This technique relies on two types of pressure gauges: a Pirani sensor and a capacitance manometer. The Pirani sensor measures pressure based on thermal conductivity and only provides accurate readings under its calibrated conditions, typically in pure nitrogen or air environments. Since water vapor has a thermal conductivity approximately twice that of nitrogen, the Pirani sensor will display lower pressure readings when water vapor is still present in the system.

In contrast, the capacitance manometer measures absolute pressure independently of the gas composition. It detects pressure changes based on physical variations in capacitance within the gauge, not on thermal conductivity. This makes it a more reliable indicator of actual pressure regardless of the vapor type present. The pressure difference test is suitable for use with various drying chambers, including manifold systems and PMMA drying chambers equipped with a heating shelf. The test can be started manually once all samples have been securely attached to the manifold and the system is properly sealed.

Figure 20: Pressure difference test available for drying chambers with shelf and manifold applications.

By comparing the readings from both sensors, the endpoint of primary drying can be determined. When the difference between the Pirani and capacitance manometer readings falls within a small range—typically between 0.025 and 0.05 mbar—it indicates that sublimation is nearly complete and primary drying has ended. To establish a reliable pressure differential for endpoint detection, multiple test runs using a representative test formulation are recommended. Additionally, before each freeze-drying cycle, a vacuum test must be performed to calibrate the Pirani sensor. This calibration is essential to ensure accurate pressure readings throughout the drying process.

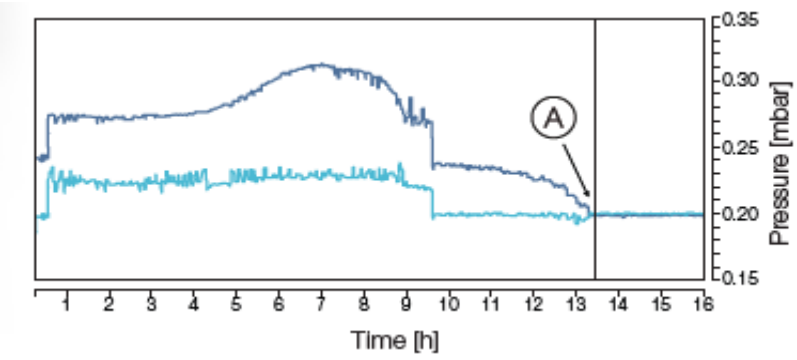

Figure 21: Pirani sensor (dark blue), capacitive sensor (light blue), endpoint of primary drying (A).

The pressure difference test has proven effective in accurately determining drying endpoints, offering clear advantages over traditional methods. It is not limited to purely aqueous samples but is also suitable for water–solvent mixtures. By precisely identifying the end of primary drying, this method enhances reproducibility and ensures product dryness by preventing premature termination of the drying process.

4.8 Temperature difference test

This test measures the product temperature using thermocouples and compares it to the set temperature of the shelf on which the product rests. During sublimation, the product temperature remains lower than the shelf temperature because heat from the shelf is required to drive the phase change. Once sublimation is complete, the product temperature rises and approaches the shelf temperature. Primary drying is considered complete when the product temperature matches the shelf temperature, typically within a difference of less than 1 °C.

Key considerations include:

- The vial containing the thermocouple may not represent the entire batch accurately due to heat conduction through the probe wire, causing the sample with the thermocouple to dry faster than others.
- When integrated into a drying program with primary and secondary phases, this test allows automatic optimization of primary drying time and smooth transition to secondary drying.
- Combining temperature measurement with the pressure difference test enhances endpoint determination, as both methods usually reach the endpoint simultaneously and offer comparable precision.
- This dual approach accommodates various sample conditions:
  - Samples that cannot hold a thermocouple rely on the pressure difference test.
  - Samples with very low initial moisture, below the detection limit of pressure sensors, are better suited for temperature-based endpoint detection.

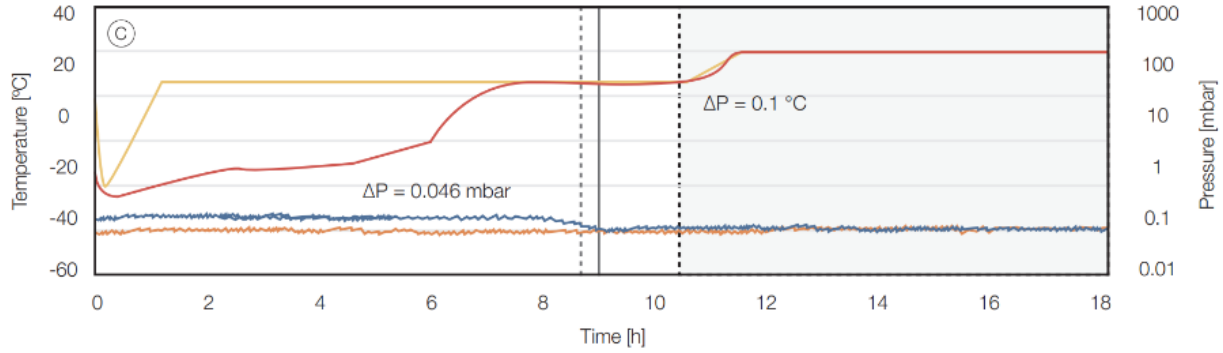

Figure 22: The freeze-drying cycle of a 50 mg/mL glycine solution was monitored using both pressure difference and temperature difference tests, with endpoint criteria set at a pressure difference of 0.025 mbar and a temperature difference of less than 0.5 °C. The graph displays the shelf temperature (yellow), sample temperature (red), chamber pressure (orange), and Pirani gauge reading (blue) throughout the primary and secondary drying phases. The time points at which the pressure endpoint (solid black line) and the temperature endpoint criterion (black dashed line) were reached are also indicated, demonstrating precise control and synchronization of drying parameters.

5. Harmonized Use of Rotavapor®, Pure, and Lyovapor™ Systems

The BUCHI systems Rotavapor® R-80/R-180, Pure Essential, and Lyovapor™ L-210/L-250 are designed to support an integrated laboratory workflow from purification to solvent removal and freeze-drying. A key advantage of this setup is the compatibility of glassware across all three systems. Standard Rotavapor® flasks can be used to collect fractions from Pure Essential chromatography, then directly transferred to the rotary evaporator for solvent removal, and subsequently to the freeze-dryer for stabilization. This reduces the need for flask transfers between steps, helping to minimize sample loss and simplify traceability across the workflow.

Figure 23: Evaporation flasks are compatible with the Rotavapor® R-80 and R-180 (left), Pure Essential (middle) and the Lyovapor™ L-210 or L-250 (right).

In addition, both the Pure Essential and Rotavapor® R-80 systems are optimized for compact benchtop use. Their small footprint allows for close placement of both instruments, saving space in the laboratory and enabling a continuous process with minimal sample transport. This configuration supports efficient use of lab resources while maintaining process integrity. The compact Lyovapor systems can be installed on a trolley to save bench space. Additionally, the outstanding cooling performance of Lyovapor™ enables the drying of high volumes of samples coming from the purification step in one freeze-drying instrument. The results are stable freeze-drying caker and complete solvent collection on ice condenser for a safe laboratory.

Figure 24: Space saving combination of Rotavapor® R-80 and Pure Essential.

6. Conclusion

BUCHI's integrated and essential solution, comprising the Rotavapor® R-80 and R-180, Pure Essential, and Lyovapor™ L-210 and L-250 systems, supports each step of the workflow, from solvent evaporation to purification and final stabilization by freeze-drying. Seamless compatibility, enabling smooth sample transitions, reduces manual handling, and maintaining high product integrity.

In addition to their technical performance, the compact footprint of the Rotavapor® R-80 and R-180, the modular stackability of Pure Essential, helps to maximize efficiency in minimal space. The safe and efficient drying process enabled by the Lyovapor™ system allows the most effective drying in a short amount of time.

By implementing this streamlined and space-conscious setup, laboratories can enhance throughput, ensure reproducibility, and future-proof their operations in increasingly demanding pharmaceutical environments.