Drying and concentration methods – an overview

Introduction

Solvent removal or concentration is an essential process for pharmaceutical, chemical and biotechnology industries, in applications where it is necessary to reduce solvent amount to a certain extend to facilitate formulation or analysis of molecules of interest. The use of drying or concentration techniques in natural products, medicinal or chemical research, and production of flavors or fragrances is quite widespread, yet, preparative purification remains their most common application.

Due to a large diversity of sample types and solvents, various commercial systems have been developed over the years to accommodate the wide range of applications - no universal solution being available at the moment.

Many drying techniques can typically meet the specificities of a given process; hence, in general, several dryer could do the job. The choice of the most appropriate solution therefore depends on several criteria, the key conditions being that the dryer must be able to handle the amount of samples required by the application, should deal with samples variations and products requirements and should carry the substance from feed to exit if necessary. As a laboratory equipment provider, BUCHI supplies several types of drying instruments - freeze dryers, spray dryers, rotary evaporators and vortex evaporators (Figure 1).

The constant development of new systems and their connected hardware – vacuum pumps, condensers, heating technologies and interfaces – is improving user interaction with the instrument, enabling the enhancement of evaporation performances, a higher sample integrity and an better solvent recovery, reducing thereby environmental impact of evaporation/concentration processes.

The use of the latest equipment, together with a good, up-to-date understanding of the process in a theoretical, applicative and practical level enables method optimization for faster sample drying or concentration.

As the market leader in the evaporation field, BUCHI offers state-of-art solutions (Figure 1). Moreover, our expertise will enable us to help you chose the most suitable solution for your application, using some important criteria such as drying time, energy consumption, scalability, productivity,... summarized in Figure 2 below.
Basic evaporation theory

Thermodynamic basics

Depending on pressure and temperature, any substance may be present in three phases – solid, liquid and gaseous. The relationship between pressure and temperature for a defined substance is shown in so-called phase diagrams (Figure 3). When a solid is being heated under constant pressure above the...
triple point, it will reach the melting point and liquefy; further heating will lead to an increase in temperature until the boiling point is reached, the liquid will then start boiling, changing into a gas\textsuperscript{1,2}. When a similar work is done with temperature and pressure below the triple point, the material will not melt but sublimate. The heat energy supplied to the sample at low-pressure transfers enough energy for thawing, however the pressure is too low for liquid formation and the solvent will therefore sublimate into gas\textsuperscript{1,2}. Since the phase of a substance is determined by both the heat and the pressure, the temperature at which boiling or vaporization occurs is set by the pressure. Reducing the pressure by applying a vacuum can therefore lead to a decrease in the solvent boiling point and to a vaporization occurring at lower temperatures. Low-pressure systems are commonly used for heat-sensitive samples, in order to decrease the boiling point so that vaporization occurs at a lower, safer temperature. Similar thinking can be done for sublimation processes\textsuperscript{1,2}.

**Drying**

Drying is the separation of a liquid from a solid. The vapor is carried away from the material and allowed to escape from the drier. When working under vacuum in a closed system or when organic solvent are used, solvents must be condensed and recovered. At the beginning of the drying process, when the product is moist enough, the speed of drying depends on vapor pressures, system pressure and on the heat supplied to the system. Once the liquid is evaporated from the surface however, there is a point where the thermal conductivity of the solid and the path of the moisture from the inside to the surface (pore structure, hygroscopic behavior) starts to have a large influence on the evaporation\textsuperscript{1}.

The vapor pressure of a solid being quite negligible compared to that of a liquid, complete separation is theoretically possible. Several difficulties might however arise when drying a solid since the product can be present in several different forms - moist solid, pulp or paste, solution, suspension... - and the most appropriate procedure should be chosen for each form\textsuperscript{1}.

**Different drying methods**

Evaporation and drying systems are some of those devices commonly found everywhere. They are of important use in lab work, mainly for applications where the main aim is to remove as much unwanted solution as possible while keeping the sample material intact. While Rotary evaporation and Vortex evaporation are mainly used in R&D and control quality for synthesis, sample preparation and extraction processes, Spray Drying and Freeze Drying can also be used in formulation in addition to the previously mentioned applications.

**Rotary Evaporator**

Rotary evaporators have been designed for quick and gentle evaporation and condensation of solvents.

They are usually used for the separation of highly volatile solvents from liquids or solids with a high boiling point. Rotary evaporation can commonly be used for solvent removal from the final stage of a reaction or the separation of mixed solvents, the precipitation of suspensions or solutions, the concentration of liquids, the re-crystallization of a sample to remove impurities, the drying of powder or granulates, the synthesis of chemicals, soxhlet extractions or solvents recycling for example.

The rotation of the sample flask increases the surface area of the mixture, thereby improving the heat transfer and making the process faster. This also makes the vaporization easier and avoids local overheating and incrustation. It also reduces retarded boiling and foaming. The vacuum lowers the boiling point, making low-temperature evaporation possible\textsuperscript{1}. 

Rotary evaporators can range in size from benchtop/lab scale instruments (200 mL – 2L) up to 20-50 L process scale units. Their main components usually are:

- A vacuum pump to lower the pressure in the system
- A heating bath to control the heating of the sample vessel
- A condenser and a chiller to condense the evaporated solvent and recover it.
- A collection vessel to recover the previously evaporated and condensed solvent
- A motor to rotate the flask and another one to lower and lift the vessel into the bath

To enable a successful evaporation performance, the rule of thumb suggests that there should be a 20°C temperature difference between the cooling and the boiling temperatures, and between the boiling and the bath temperatures. Recommended parameters would be 20/40/60°C, however this could be modified when the product must not be heated to 40°C or whenever solvent boils at a temperature lower than 40°C under atmospheric pressure. The vacuum and cooling conditions are ideal when the condensate covers approximately half to three quarters of the height of the condenser.

Many criteria will then determine the choice of the most appropriate rotary evaporation solution for a process. A wide range of solutions covering essential needs, as well as specific demands can be found.

For concentration or solvent recycling to drying or continuous evaporation of large volumes, Industrial Rotary Evaporation solution such as BUCHI Rotavapor R-220 Pro (Figure 4) and R-250 will enable to process up to 30L of solvent in a 50L flask. Both instruments also exist in an explosion proof version. Moreover several accessories, extension option and customization compatible on Industrial Evaporation units are available to match customer specific needs.

For evaporation, concentration or drying at laboratory scale, BUCHI benchtop rotary evaporator (Rotavapor R-300 - Figure 5) meet application specific needs with a wide range of tailor-made solutions covering essential needs, as well as highest demands in convenience and productivity. For example, the conjunction of the foam sensor and the Interface I-300 / I-300 Pro enables unattended distillation of foaming samples. The sensor automatically aerates the system temporarily to avoid extensive foam formation, while keeping the vacuum on a constant level.

When many samples need to be concentrated or dried, systems that evaporate in parallel could be more adequate than rotary evaporation. Vortex evaporators systems are essentially similar than rotary evaporator but they allow the evaporation of several sample in parallel.
**Vortex Evaporator**

These evaporators are boiling samples under vacuum, while swirling the tubes to create a vortex. The vortex increases the surface area for evaporation, improving the heat transfer and making the process faster. Heating can be supplied by heating lamps directly over the product, through a heating medium and/or using heating block around the tubes. The swirling movement cannot prevent solvent bumping and therefore careful attention must be paid to avoid sample loss or cross contamination along the process\(^2\)-\(^4\).

In a similar way than for the rotary evaporator, the \(\Delta T=20^\circ C\) rule was slightly modified into the \(\Delta T=25^\circ C/20^\circ C\) rule and is a good starting point for vortex evaporation processes and the condensate should approximately reach half to three quarters of the height of the condenser when vacuum and cooling conditions are ideal\(^3\),\(^4\).

BUCHI vortex evaporator solutions enable to concentrate or evaporate multiple samples to dryness in parallel facilitating screening or sample preparation in R&D or quality control for example. The Multivapor (Figure 6) enables the concentration of a sample to a defined volume\(^3\), while the Syncore Analyst (Figure 7), with the cooled appendix was developed to evaporate to dryness or to handle heat-sensitive samples\(^4\). The Syncore Polyvap, with heated cover is recommended in case of high-boiling solvents\(^4\).

**Spray Dryer**

Spray Drying is a widely applied method to convert aqueous or organic solutions, emulsions, dispersions and suspensions into a dry powder. Applications are found in all major industries ranging from industrial chemistry, pharmaceutical, biotechnology, cosmetics to food industry. Dry milk powder, instant soups, instant coffee, detergents and dyes are just a few examples of spray dried products currently available in everyday life\(^1\).
Spray drying is accomplished by dissolving, emulsifying or dispersing the core substance in a solvent or in a solution of carrier material. The material is then atomized and sprayed into the drying chamber where a hot stream of drying gas will help evaporate the solvent to produce dry solid particles that will further be separated from the gas stream and collected\textsuperscript{1,5,6}.

The process parameters, the properties of the feed and the equipment design are variable that can be adjusted to modify the characteristics of the final product.

BUCHI Mini Spray Dryer (Figure 8) is a laboratory scale spray dryer integrating a two-fluid nozzle that uses compressed gas (normally air or N\textsubscript{2}) to disperse the liquid body into fine droplets which are subsequently dried in the cylinder. The powder collection is provided by a cyclone separator which works by centrifugal forces using the inertia of the solid particles.

Spray drying can be considered a high throughput process since it is drying very quickly compared to other drying techniques. It provides the advantage of weight and volume reduction. The transformation of a liquid product into a dry powder is done in a single step, which makes the method advantageous in terms of costs, scale-up and process simplification. The powder can be fully engineered and processed into tablets/capsules without milling or other secondary processing, moreover, most temperature sensitive substances like enzymes, proteins, antibiotics, etc. can be spray dried without major loss of activity\textsuperscript{1,5-9}.

Due to a loss of product on the wall of the drying chamber and into the exhaust air, yields in laboratory scale experiments are far from optimal and are reported to be in the range of 20-70\%\textsuperscript{5-7}. At industrial scale however, yields increase with larger scale setups since the lost fraction is a smaller part of the production volume. Insufficient forces of liquid atomization and the ineffectiveness of the cyclone to effectively separate fine particles with a diameter below 2 μm, makes the production and the recovery of sub-micron particles tedious. This phenomenon has to be considered in the development of drug delivery systems such as intravenous administrated pharmaceuticals\textsuperscript{5-7}. Laboratory scale spray drying also fail to produce particles with a size range above 50 μm – similar to those produced at large scale. This needs to be taken into account during lab scale screening since it could lead to some issue later during scale up when dissolution profile of particles and powders are important parameters.

**Freeze Dryer**

Freeze-drying or lyophilization is an effective way of drying a material. It is using the physical principle of sublimation, which involve the direct transition between the solid and the gaseous phase, bypassing the liquid phase. The frozen sample is dried under vacuum without being allowed to thaw. This process is suitable for a wide range of applications such as the preservation of delicate material against degradation or decomposition, the preservation of product characteristics and initial shape, the conservation of products that require fast rehydration or the conditioning of product for further use. Vaccines, dried fruits and vegetables, dried mushrooms or soluble coffee are common freeze-dried products available in everyday life\textsuperscript{10}.

The crucial parameters in freeze drying are pressure and temperature. A typical freeze drying process involves two stages – freezing and primary drying. For some samples a secondary drying might be required in order to remove solvent molecules tightly attached to the sample and reduce moisture
further. Each process step has distinctive requirements in terms of pressure and temperature depending on sample characteristics.

Most liquid products, or formulations, freeze by forming ice crystals. Size and shape of the ice crystals depend on the cooling speed and define the freeze drying ability; rapid cooling results in small ice crystals while slower cooling leads to larger ice crystals. In terms of freeze drying, small ice crystals are more challenging to remove from the product than large ones. Yet, the freezing temperature of a formulation is defined by its characteristics and composition.

Formulations can generally freeze in two different ways; eutectic mixtures contain substances that freeze at lower temperatures than the water surrounding them. When cooling an eutectic mixture, water is the first to separate from the substances and it freezes to ice. The formulation may now appear frozen but the remaining substances are actually still liquid. They form concentrated areas that freeze eventually at temperatures below the freezing point of water. The temperature where all components of the mixture are properly frozen is called eutectic temperature. This is the critical temperature of the formulation and the maximum temperature the formulation can endure during the freeze drying process. Applying vacuum to an incompletely frozen eutectic mixture, may result in the destruction of the product as unfrozen components expand when placed under vacuum.

The other class of mixtures is amorphous and form glassy states when frozen. With decreasing temperature, the formulation becomes more and more viscous and eventually freezes to a vitreous solid at the glass transition point. For amorphous products, the critical point in terms of stability is called collapse temperature. The collapse temperature is typically slightly lower than the glass transition point. Amorphous products are generally very challenging to freeze dry.

The first drying phase – the primary drying - removes the bulk of water within the product by sublimation. The temperature of the product is defined by the pressure in the drying chamber and the heat input must be carefully controlled. The ideal product temperature is as high as possible to maximize the vapor pressure difference between the sample and the condenser, though at the same time it must remain below the product’s critical temperature to preserve the frozen character. By using heated shelves, the set temperature is slowly approached at a defined heating rate.

The vast majority of the water should be removed by the end of the primary drying phase. The residual moisture content of the product may now be 5 – 10% due to water bound to the matrix. At this stage, ice should not be present anymore. The secondary drying step removes the adsorbed water molecules by desorption. In order to achieve ideal conditions for desorption, the lowest possible pressure as well as a further increase of the shelf temperature is required. Again, product stability must be considered when choosing the shelf temperature. Secondary drying is usually performed for shorter time periods.

At the end of secondary drying, the product moisture content should be in the range of 1 – 5%.

BUCHI offers two different platforms for Freeze Drying - the Lyovapor™ L-300 and L-200 (Figure 9). With its dual condensers at -105°C, the Lyovapor™ L-300 offers infinite ice capacity, essential Freeze Drying for water and organic based solvents regardless of how large the sample throughput is. It was recently shown that BUCHI Lyovapor L-300 could sublime 9 L of a
mixture of 50:50 Acetonitrile:Water in 20 hours. This very fast process time is due to the lack of ice insulation in the condenser thanks to the automatic steam cleaning of one of the condenser while the other is being used. The L-200 is a compact, high quality freeze drying unit, with a high level of automation. With 6 kg/55 °C condenser, control unit, vacuum pump and vacuum regulation, the Lyovapor™ L-200 efficiently covers the main requirements of Freeze Drying. Based on those platforms, individual solution can be specifically and precisely adapted to the various requirements of the users in order to achieve the greatest possible efficiency.

Freeze drying is usually the favorite choice for the preservation of a wide range of pharmaceutical, mainly when stability in the liquid state is not adequate, storage requirements are too rigorous or when the product is required in solid form. It is well suited for formulations that do not require further processing after drying since they can be filled directly in vials, which can be sealed in the drying after the cycle, in order to avoid potential contaminations. Freeze drying strengths lie in the low process temperatures, high yields, great product uniformity and often, high quality in term of activity, water content and/or stability. The accurate control of the process enables the production of a product of the highest quality since it minimizes risk of intrinsic products properties such as collapse, eutectic melt or glass transition temperatures being exceeded\textsuperscript{8,9}.

Even though freeze-drying shows non-negligible benefits for sensitive products, industries are investigating alternative methods such as spray drying, due to the high cost, long process time and limited volumes associated with lyophilization at production scale.

Conclusion

Nowadays, a wide range of evaporation and drying systems are commercially available in order to accommodate the large range of application requiring solvent removal. To select the best method, not only application feasibility must be considered but also drying cost in term of energy consumption and drying time. Last but not least, a good understanding of the processes and factor affecting it helps to apply the selected drying method to its full capabilities. Laboratory scale units are important as screening instrument in order to become familiarized with samples and understanding their behavior in defined conditions. As the market leader in the evaporation field, BUCHI offers state-of-art solutions and a high expertise to enable customer to choose the most suitable solution for their applications.

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