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Peter Froelich, President
Peak Media, Franklin, MA

Judy Silva, Marketing Communications Manager
Parker Hannifin Corporation
Filtration and Separation Division
Haverhill, Massachusetts

In-house generation of gases for analytical instrumentation such as nitrogen for liquid chromatography with mass spectroscopic (LC-MS) detection provides a number of benefits including a significant increase in laboratory safety and a reduction in cost compared to providing the gas via high pressure tanks. An in-house generator isolates nitrogen from ambient air using a membrane that allows oxygen and water vapor to permeate the membrane and allows the nitrogen to pass to the detector. This system operates at a low pressure and permits the chromatographer to operate the system on a 24 hour/7 day basis without the inconvenience and hazards of replacing tanks. In addition, the use of an in-house generator requires a significantly smaller energy input than the use of heavy tanks which must be transported from the facility where they are filled to the end user and then returned.

Modern analytical instrumentation requires a variety of highly purified gases such as nitrogen, hydrogen, ultra-dry air, zero air and purge gas. As an example, Liquid Chromatography with Mass Spectroscopy (LC-MS) detection is commonly employed for the qualitative and quantitative analysis of a broad range

of complex samples in environmental and pharmaceutical studies. The technique requires that the mobile phase be evaporated by nebulization after the sample is separated. Nebulization is performed using nitrogen (typically a flow of 7-15 L/min is required). The required flow can be provided in a number of ways including the use of an in-house generator, the use of pressurized tanks or the evaporation of liquid nitrogen.

In recent years, many laboratories have found that the use of an in-house generator is the method of choice to supply the required gases (e.g. high purity nitrogen for LC-MS). An in-house generator can provide the necessary gas at the pressure and flow required by the application on a 24 hour/7 day a week basis with a significant increase in safety and convenience, coupled with a reduction in cost. In this white paper, we describe how high purity nitrogen can be generated in the laboratory and outline the various benefits of this approach for LC-MS detection.

In-house generation of nitrogen

In-house generation of nitrogen from compressed ambient air involves the separation of the gas from oxygen, water vapor and particulate matter and porting it directly into the LC-MS system. The compressed ambient air is initially filtered using a high efficiency activated carbon filter to remove hydrocarbons and a pre-filtration system is employed to remove particulate matter down to 0.1 micron. The air is then delivered to a fiber membrane bundle which is the heart of an in-house nitrogen generator. The membrane bundle permits oxygen and water vapor to permeate the membrane and escape through the sweep port while the nitrogen flows through the

tube (Figure 1). While each individual fiber membrane has a small internal diameter, a large number of fibers are bundled together (Figure 2) to provide an extremely large surface area for the permeation of oxygen and water. The nitrogen is passed through another membrane filter and then delivered directly to the LC-MS.

An in-house nitrogen generator such as the Parker Balston N2-45 (Parker Hannifin, Haverhill, MA) can produce pure nitrogen on a continuous basis. The purity of the nitrogen is dependent on the operating pressure and the desired flow rate; as an example, 67 L/min of 99.5% nitrogen gas can be generated using an operating pressure of 145 psi at 68°F, which is sufficient to supply the gas to several LC/MS systems. Table 1 provides a comparison of the flow rate that can be obtained at various levels of purity at different input pressures (if desired, an optional oxygen analyzer which monitors the oxygen content of the stream can be fitted on the in-house nitrogen generator).

The gas that is delivered to the LC-MS by the N2-45 generator has an atmospheric dew point of -58°F (-50°C), contains no particulate matter > 0.01 micron, is hydrocarbon and phthalate free and is commercially sterile.

A broad range of other high purity gases can be readily generated in-house, for example hydrogen can be obtained via the electrolysis of water, while zero air is prepared by passing filtered air over a heated catalyst to remove trace hydrocarbons by converting them into CO₂ and H₂O.

Table 1 Flow Rates for Various N₂ Purity Levels (N2-45 Nitrogen Generator, 35°C)

Desired Purity	Input 145 psi	Input 125 psi	Input 110 psi	Input 100 psi	Input 90 psi	Input 80 psi
99.5 %	67 L/min	55 L/min	47 L/min	39 L/min	33 L/min	27 L/min
99.0 %	92 L/min	74 L/min	63 L/min	53 L/min	44 L/min	35 L/min
98.0 %	129 L/min	106 L/min	89 L/min	73 L/min	62 L/min	50 L/min
97.0 %	163 L/min	132 L/min	113 L/min	94 L/min	79 L/min	65 L/min
96.0 %	200 L/min	160 L/min	137 L/min	114 L/min	97 L/min	80 L/min
95.0 %	233 L/min	187 L/min	160 L/min	134 L/min	111 L/min	90 L/min



Figure 1: Hollow fiber membrane bundle separates nitrogen from air. Oxygen and water vapor permeate the membrane, allowing nitrogen to flow through the tubes.

Safety benefits of in-house generation of nitrogen

In-house generation of gases provides a significant number of safety related benefits, including:

- An in-house generator generates only a small amount of gas in a given time period and the amount can be controlled by the user. As an example, the Parker Balston N2-45 nitrogen generator can provide a maximum flow of the gas of 133 L/min at a maximum pressure of 140 psig. In contrast, a standard compressed nitrogen tank has an interior pressure greater than 2000 psi when full.

If a leak were to occur in the system when an in-house generator is employed, only a small amount of gas would enter the lab. However, if a compressed gas tank is used to supply the nitrogen and a leak occurs in the tank, valve or the tubing connecting the tank to the LC/MS, a significant amount of nitrogen would be rapidly expelled into the laboratory. This gas would displace the equivalent amount of air and could lead to the asphyxiation of laboratory personnel.

- When an in-house generator is employed, a permanent connection to the LC-MS system is made. In contrast, when a tank is used to supply the gas, it must be replaced on a periodic basis. It is necessary to transport full tanks from the storage area (which is frequently outside) to the area of use. Tanks are bulky and heavy; if an accident occurred; a rapid depressurization of the tank could result in injury to personnel and/or damage to the laboratory.

- If liquid nitrogen is used to provide nitrogen gas, the operator needs to take precautions to avoid potential leaks in the system to ensure that a significant amount of gas does not escape into the laboratory. In addition precautions should be taken to avoid freeze burns as the temperature of liquid nitrogen is -196°C .

In-house generation of nitrogen is more convenient

- When an in-house nitrogen generator is employed, the gas is supplied on a continuous 24 hour/7 day a week basis without any user interaction. In contrast, when tank gas is employed, the user must pay close attention to the level of gas in the tank and replace the tank on a periodic basis.

- In many facilities, spare gas tanks are stored outside in a remote area for safety reasons and it can be time consuming to get a replacement cylinder.

- When it is necessary to get a replacement nitrogen gas tank, the laboratory manager may need to use an individual who is qualified to handle the tanks. Many chromatographers have indicated that replacing used tanks can be a significant inconvenience, especially in inclement weather if the tanks are stored outside, or if they are not secured properly when the laboratory is located in a seismic zone.

- If tank gas is used to supply the nitrogen and the need for replacement occurs during a series of analyses, the analyst must interrupt the analytical work, replace the tank, restart the system and wait for a stable baseline. In addition,

it may be necessary to recalibrate the system. Since an in-house generator can supply nitrogen on a 24 hour/7 day basis, interruption of a series of analysis is not an issue and laboratory throughput is increased.

- If a series of automated analyses is desired (i.e. on an overnight or weekend basis), the analyst must ensure that sufficient volume of gas is on hand before starting the sequence. This can be an issue if tank gas is used, but since the in-house generator can supply nitrogen on a 24 hour/7 day basis, this is not an issue.

- The frequency of tank replacement clearly depends on the usage of the system. Changing the tank leads to a reduction in the useful operating efficiency of the facility. In addition to the actual time required for changing of the tank, the laboratory staff must verify that there are sufficient replacement tanks in storage and order replacement tanks as appropriate. The use of an in-house generator eliminates the need to keep track of and change gas cylinders.

- An in-house generator requires minimum maintenance. Most users find that the only requirement is that the filters are changed approximately once a year.

- An in-house nitrogen generator monitors the flow and/or the pressure of the gas. If there is a significant increase or decrease in the flow and/or pressure of nitrogen, a signal can be sent to the LC-MS to stop analyzing samples so that invalid data is not collected. This feature is especially important when the analyst is working with a sample that is difficult to reproduce or is working with a high value sample.

In-house generation allows for control of oxygen content of the gas

The presence of oxygen in the nitrogen used for LC-MS can have significant effect on the sensitivity of the detector:

- When an Atmospheric Pressure Chemical Ionization (APCI) interface is employed, it has been found that raising the oxygen content can increase the sensitivity of the detector.

- The presence of oxygen in the mass spectrometer may lead to undesirable ion reactions which could make interpretation of the data more difficult.

- If tank gas is used, the gas is normally of extremely high purity and the oxygen content is fixed. If it is necessary to change the oxygen content,

Table 2 Annual Costs, In House Generation of Nitrogen versus the use of High Pressure Tanks (in US \$)

	In-House Generator	Tanks
Electrical Power	\$100	\$0
Maintenance	\$800	\$0
Cylinders	\$0	\$3,120
Demurrage	\$0	\$840
Labor (changing cylinders)	\$0	\$1040
Order Processing	\$30	\$360
Shipping	\$50	\$3,720
Invoice Processing	\$10	\$120
Inventory Control	\$0	\$72
Total	\$890	\$9272

Assumptions:

- 52 cylinders at \$60/cylinder
- 10 cylinders in use (5 in use, 5 filled) at \$7/mo
- \$30 labor/cylinder
- 1 order/month @ \$30 processing costs
- Labor \$20/cylinder change

a significant amount of additional plumbing may be required to provide both gases to the detector. When an in-house generator is employed, it is easy to change the oxygen concentration by simply changing the pressure of the input gas.

In-house production of nitrogen is less expensive than the use of gas tanks

An important benefit of an in-house generator is the significant cost reduction relative to the use of gas tanks or liquid nitrogen. The running cost of operation of an in-house generator is extremely low; as the raw materials to prepare the required gas are air and electricity (if the optional oxygen analyzer is employed, the electrical requirement is 25W or approximately 0.6 kW/ 24 hour day). In contrast, the overall cost for using nitrogen gas from tanks includes the actual cost of obtaining the gas tank as well as the time involved in changing tanks, ordering new tanks, maintaining inventory, and related activities. In addition, when tank gas is employed, the user must include the cost of the lost productivity due to down time from changing of tanks and recalibrating the system.

The calculation of the precise cost of the use of nitrogen gas from tanks for a given user is dependent on a broad range of local parameters and the amount of

gas that is used. It should be noted that there are many hidden costs, including transportation costs, demurrage costs and the paperwork (e.g. a purchase order, inventory control and invoice payment) when tank gas is employed. In addition; the value of the time that is required to transport the tank from the storage area, install the tank, replace the used tank in storage and wait for the system to re-equilibrate after the tank has been replaced costs money as well.

A comparison of the cost of supplying gases via tanks versus the cost for use of in-house gas generator is presented in Table 2. In this analysis, we assumed that a single tank of gas is consumed each week and assume that the cost of each tank is \$60 (this approximation ignores the incidental cost of handling the gas tank, down time, ordering tanks, etc.). In comparison, the cost of using the in-house generator is approximately \$20 per week.

In-house generation of nitrogen reduces overall energy consumption

When tank gas is employed, the nitrogen must be isolated from air via fractional distillation, an energy intensive process. After the tanks have been filled, they must be transported to the user site (and the empty tanks returned), expending a significant amount of energy. The use

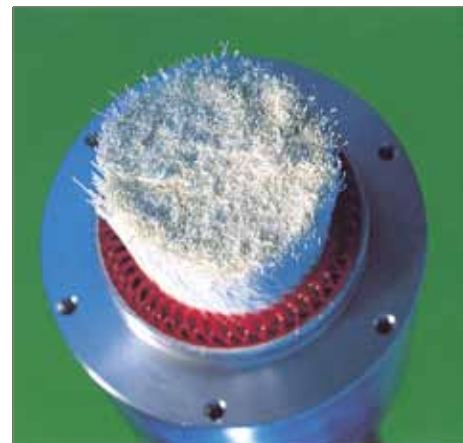


Figure 2: A large number of fibers are bundled together to provide an extremely large surface area for the permeation of oxygen and water.

of an in-house generator with a hollow fiber membrane for the generation of nitrogen utilizes significantly less energy and hence generates less greenhouse gas than fractional distillation and no transportation of heavy bottles is required.

Conclusions

In-house generation of nitrogen can provide the necessary gas for LC-MS systems with a significant increase in safety and convenience compared to the use of tank nitrogen or liquid nitrogen and a Dewar flask. In addition, the overall cost is dramatically lower and the operator can rapidly change the composition of the gas by simply varying the input pressure to optimize sensitivity of the analytical procedure. An in-house nitrogen generator can provide the desired gas on a 24 h/day, 7 day/week basis from compressed air using a hollow fiber membrane which permits oxygen and water vapor to permeate the membrane and escape through the sweep port while the nitrogen flows through the tube into the LC-MS system. Other gases commonly required by the analytical laboratory can be readily generated in house, similarly providing dramatic increases in safety and convenience, with a significant reduction in cost.



Parker Hannifin Corporation
 Filtration and Separation Division
 242 Neck Road
 Haverhill, MA 01835
 1-800-343-4048, 1-978-858-0505

LCMS Nitrogen White Paper
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