Preparation of a new hollow fiber cartridge

Preparing a cartridge for use

A new ultrafiltration (UF) cartridge must be flushed with water to remove the preservative solution and to wet out the media; a new microfiltration (MF) cartridge must be wetted out. The following list summarizes the preparatory steps, many of which are optional. Used cartridges are prepared in the same way.

1. Flush or wet out the cartridge—before using a new ultrafiltration cartridge or reusing an ultrafiltration or microfiltration cartridge from storage, flush the preservative from the cartridge. A new microfiltration cartridge must be wet out.
2. Determine the cartridge's water permeability—determine the cartridge's permeability by measuring water flow through it under controlled process conditions. By measuring the cartridge's permeability before and after use, a benchmark is created that determines cleaning effectiveness and monitors performance.
3. Optional alcohol pretreatment and water presoak—tight ultrafiltration cartridges (30,000 NMWC and lower) benefit from presoaking in alcohol. Autoclavable and steam-in-place cartridges benefit from an extended water soak.
4. Install cartridge and test system for integrity—check the system for leaks and cartridge for integrity.
5. Sanitize or depyrogenate the cartridge—when sanitary conditions are required, sanitize or depyrogenate the cartridge by circulating sanitizing/depyrogenating agents through it.
6. Condition the system with buffer—conditioning exposes a separations system's wetted parts to an appropriate buffer before introducing product to the system. The conditioning minimizes unwanted chemical reactions between product and the wetted parts.
7. (If desired) Clean, maintain and store the cartridge.

Flushing and pretreatment considerations

Ultrafiltration

Removal of glycerol preservative

New ultrafiltration membrane cartridges are pretreated with an alcohol/glycerol solution within the pore structure to prevent drying of the membrane. This mixture enhances wetting but may cause the fibers to appear wavy. Trace amounts of isopropyl alcohol (IPA) may remain when the cartridges are shipped, and the glycerol must be thoroughly rinsed from the cartridge prior to use. In addition to the prevention of drying, the glycerol minimizes entrained air within the pore structure of the membrane. The air may become "locked-in," reducing permeability until the air has been displaced by liquid. Glycerol removal and wetting out will occur simultaneously when performing the new cartridge rinsing procedure.

New cartridge rinsing procedure (recommended for all membranes)

The new cartridge rinsing procedure should be performed on all ultrafiltration cartridges.

1. Install the cartridge and connect to system.
2. Connect the retentate and the permeate lines to an appropriate waste container.
3. Fill the feed reservoir with clean water (WFI or 10,000 Nominal Molecular Weight Cutoff [NMWC] UF permeate). Use room temperature or warm (up to 50°C [122°F]) water for rinsing. Cold water will be less effective. Addition of 100 ppm NaOCl to rinse water will enhance glycerol removal.

4. Start the pump on slow and adjust transmembrane pressure (TMP) to:
   - 1 barg (15 psig) for 1,000 NMWC and 3,000 NMWC pore sizes
   - 0.7 barg (10 psig) for 5,000 NMWC through 50,000 NMWC pore sizes
   - 0.3 barg (5 psig) for larger pore sizes
5. To reduce water consumption, set the pump speed and retentate back pressure such that retentate flow rate is approximately 1/10th of the permeate flow. The pump speed will be set quite low as most of the fluid is passing through the membrane as filtrate.
6. Add more fluid to the feed reservoir, as needed.
7. Continue rinsing for 90 minutes.
8. If NaOCl is used, thoroughly rinse cartridge before introducing solution.

Autoclavable/steam-in-place cartridges (extended presoak)

Before sterilizing UF cartridges in an autoclave or in an SIP sterilization procedure, the cartridge must be fully rinsed of glycerol. If UF cartridges are to be autoclaved or steam sterilized, a presoak is recommended as an adjunct to the flushing procedure.

1. Rinse cartridge per new cartridge rinsing procedure, above, for 30 minutes.
2. Soak cartridge in clean water at least four hours, and preferably overnight. Be certain that both the lumen side and shell side of the cartridge are filled and that air has been displaced.
3. Rinse cartridge per new cartridge rinsing procedure for 30 minutes.

Used ultrafiltration cartridge flushing procedure

Cartridges stored with water

If ultrafiltration cartridges are stored water-wet for short-term storage, flush water through the cartridge using the new cartridge rinsing procedure. However, in this case, circulate the water for a minimum of 10 minutes to wet the cartridge out.

Cartridges stored with preservative

Flush used cartridges stored with a preservative solution with a 100 ppm sodium hypochlorite solution. Then flush water through the microfiltration cartridge using the new cartridge flushing procedure described in the new cartridge rinsing procedure [recommended for all UF membranes].

Microfiltration

Although microfiltration membrane cartridges are shipped dry, without preservative solutions, it is prudent to rinse cartridges before first process exposure or heat sterilization. Follow the new cartridge rinsing procedure for at least five minutes at 0.3 barg (5 psig) inlet pressure. Longer flush times may be required, depending on the cartridge size.

Preconditioning

Prior to introducing the feed stream into the system, it is best to equilibrate the wetted areas (including the cartridge) with a solution that contains the same electrolytes as the feed stream. After the glycerol rinse or water flux test, rinse the system for 10 minutes with the appropriate buffer.

Optional alcohol pretreatment procedure

Alcohol pretreatment (for low molecular weight cutoff ultrafiltration membrane cartridges)

Alcohol pretreatment may be used to enhance water flux of "tight" (30,000 NMWC and lower) UF membranes. For best results, follow procedure below before water contact, extending time of soak to overnight. If cartridge has already been exposed to water, shake out excess and then extend the alcohol soak time to overnight. Either isopropyl alcohol (IPA) or ethanol may be used.

1. Fill cartridge with 100% alcohol for one hour. For best results, soak cartridge overnight. Be certain that both the lumen side and the shell side of the cartridge are filled and that air has been displaced. This procedure will be more effective if the alcohol is pumped through the cartridge at 0.34 barg (5 psig) TMP for at least 10 minutes prior to soaking.
2. To remove alcohol, rinse with clean water according to the new cartridge rinsing procedure.

The alcohol solution may be saved and reused several times before discarding.

All of these recommendations are simply guidelines for first time users. They are not intended to supersede any established standard operating procedure (SOP) that has been adopted for a validated process.

Install cartridge and test system for integrity

In this preprocessing step, check the system and the cartridge for leaks or damage as follows:

1. Check the system for leaks.
2. Test cartridge integrity to ensure it is sound.

To check the system and cartridge, perform the pressure hold test described below for a qualitative measure of integrity. If a quantitative approach is required, please refer to the *Integrity Testing Handbook*. In this handbook, the air diffusion test for

ultrafiltration cartridges and the bubble point test for microfiltration cartridges are detailed.

Pressure hold test

A schematic diagram for a typical pressure hold test system is provided in Figure 1. Step-by-step instructions for pressure hold testing follow.

1. A new ultrafiltration cartridge should be flushed of its glycerol preservative solution and fully wetted. Ultrafiltration or microfiltration cartridges that have been used should be thoroughly cleaned, flushed, and fully wetted.

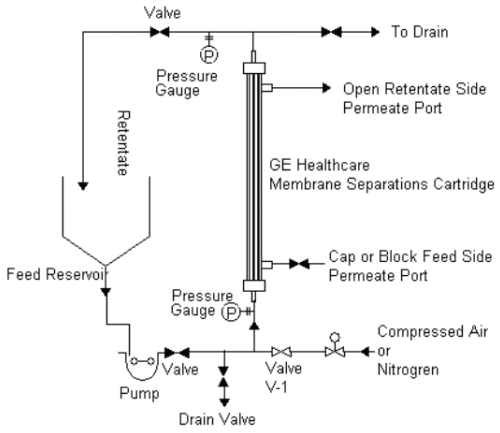

Figure 1. Typical pressure hold test apparatus setup

2. Drain cartridge of excess liquid (but see observation method B, under 7, below; if using this method, fill the cartridge with water).
3. Close all valves.
4. Leave top permeate port open to atmosphere. Block or cap feed side permeate port.
5. Adjust air inlet pressure to about 0.2 barg (3 psig) and open valve V-1.

   NOTE: When air pressure is first applied, trapped air on the permeate side will cause bubbles to appear. These bubbles should dissipate within a few seconds and the test should proceed. However if bubbling continues at this point, the test should be aborted. Stop the test and rewet the cartridge. Under the rare occasion that bubbling should occur upon pressurization to 0.2 barg (3 psig), the test should be discontinued and GE Healthcare personnel should be consulted.
6. After initial bubbling subsides, increase air pressure to ~ 0.3 barg (~ 5 psig). It is possible that additional bubble movement will reappear at this point. Allow a few seconds for this minor bubbling to stop.
7. Maintain pressure at about 0.3 barg (5 psig) for one minute. If only small bubbles from air diffusion are observed, membrane cartridge is integral.

   NOTE: The point of observation will vary depending on your setup. Three primary means of integrity determination are as follows:

   A. Close the air/gas inlet, then monitor the pressure gauge for a significant decrease in pressure.

   B. (For cartridges with clear housings) Observe the evolution of a steady stream of bubbles when the cartridge is filled with liquid.

   C. Connecting tubing to the upper port, submerge the other end in a vessel of water and look for significant bubbling in the vessel.
8. Look and listen for air leaks at all piping joints. If uncertain of a leak, wet area with a soap solution and look for bubbles. Tighten or replace any suspect fitting or tubing.
9. Release pressure by closing pressure regulator and slowly opening retentate valve. It is important not to shock the cartridge.
10. Reset valves to proper position for next operation.

Refer to filter integrity testing publications for more detail.

When using a peristaltic pump on a system, it is often convenient to use this device as the source of air pressure.

1. Fully drain the reservoir.
2. Drain cartridge.
3. Close all valves.
4. Leave top permeate port open to atmosphere. Block or cap feed side permeate port.
5. Operate the pump at a low speed while watching the inlet pressure gauge. When it reaches 0.2 barg (3 psig), stop the pump.
6. After initial bubbling subsides, operate the pump to reach an air pressure reading of 0.3 barg (~5 psig). It is possible that additional bubble movement will reappear at this point. Allow a few seconds for this minor bubbling to stop. Stop pump to hold 0.3 barg (~5 psig).
7. Maintain pressure at about 0.3 barg (5 psig) for one minute. If only small bubbles from air diffusion are observed, membrane cartridge is integral.
8. Look and listen for air leaks at all piping joints. If uncertain of a leak, wet area with a soap solution and look for bubbles. Tighten or replace any suspect fitting or tubing.
9. Release pressure by slowly opening retentate valve. It is important not to shock the cartridge.
10. Reset valves to proper position for next operation.

Permeability (water flux) determination

Clean water flux evaluation

Cartridges can be reused if they are properly cleaned and stored. However, after a number of uses/cleaning cycles, the permeability performance of the cartridge may decrease to an undesirable level. Thus, it is important to determine the cartridge's permeability while the cartridge is new, because by comparing the permeability of the cartridge over time, it is easier to determine when the cartridge should be replaced. To monitor the performance of the cartridge and the effectiveness of each cleaning, measure the permeability of the cartridge after each cleaning and compare that figure with the cartridge's performance when new.

Obtaining baseline data on a new cartridge

After rinsing, the next step with a new cartridge is to obtain baseline data on clean water flux. This is accomplished by:

- Measuring the flow rate of clean water through the cartridge at a low steady pressure
- Measuring the temperature of the water
- Calculating the flux—water flow rate in liters per square meter of membrane area per hour (lmh)
- Normalizing the permeability value to 25°C (77°F)
- If the cartridge is new, record the permeability data for later use. If checking the permeability of a used cartridge, record and compare the data to previous permeability data. Baseline data should be taken under easily repeatable conditions so that comparisons with water flux data after cleaning cycles can be made directly. The parameters to reproduce are:
  - Water temperature
  - Cartridge inlet pressure
  - Cartridge outlet pressure
  - Permeate pressure

"Clean" water, which is defined as 10,000 NMWC (or tighter) ultrafiltration permeate, or WFI, is required to assure contaminants are not present which could negatively impact membrane performance.

Water flux is most reliably measured at low pressure. When using UF permeate or WFI, minimal cross flow is required, and the retentate valve need only be cracked open to ensure elimination of air trapped on the lumen side.

With high flux GE Healthcare MF and ≥500,000 NMWC UF membranes, parasitic pressure drop will occur on the permeate side of the cartridge during clean water flux determinations unless the inlet pressure is very low (typically <0.3 barg [5 psig]) and there are no restrictions (flowmeter, reducers, etc.) on the permeate piping. Thus, while a laboratory scale membrane operating under ideal conditions might exhibit a water flux of 50 liters per square meter of membrane surface area per hour per psig [lmh/psig], the same membrane in a process scale cartridge might exhibit a slightly lower clean water flux of 25 lmh/psig.

Again, as long as the operating conditions and piping are kept consistent, water flux data over the life of the cartridge can be monitored and compared.

Procedure for measuring water flow and calculating the flux

1. Fully open permeate valve.
2. Crack open the retentate valve.
3. Start the feed pump, increasing flow to a feed pressure of 0.07 to 0.3 barg (1 to 5 psig) for microfiltration cartridges and 0.3 to 1.7 barg (5 to 25 psig) for ultrafiltration cartridges. The objective is to attain a consistent, measurable permeate flow.
4. Measure the permeate flow in ml/min and calculate the flux in l/m²/hr; see Equation 1.
5. Measure the temperature of the water.
6. Record pressures, flow rates, and temperature on a data log form.
7. Normalize the flux temperature to 25°C; see Equation 2.

As a convention, flux is recorded in terms of liters per square meter of membrane surface area per hour (lmh) or gallons per square foot of membrane surface area per day (gfd). Flux in lmh is:

Equation 1

$$\text{Flux (lmh)} = \frac{\text{Permeate flow (ml/min)}}{\text{Cartridge area (m}^2\text{)}} \times 0.06$$

Example:

For cartridge model number UFP-10-C-5A containing 0.2 m² of membrane surface area, a permeate flow rate of 200 ml/minute at a given operating pressure calculates to a flux of 60 lmh:

$$\text{Flux} = \frac{200 \text{ ml/min}}{0.2 \text{ m}^2} \times 0.06 = 60 \text{ lmh}$$

Over a narrow range (e.g., 25°C ± 10°C [77°F ± 20°F]), changes in water viscosity may be approximated by the ratio of temperature change in degrees Fahrenheit. Thus, water flux or process flux measurements between runs may be easily compared at a standard temperature, using Equation 2.

Equation 2

$$\text{Temperature corrected flux} = (\text{Flux})T2 \times \frac{T1}{T2}$$

where

T1 = Reference temperature (e.g., 25°C)

T2 = Actual temperature (°C)

Example:

On a new cartridge, the measured clean water flux is 60 lmh at 18°C (64.4°F).

Temperature corrected flux =

$$60 \text{ lmh} \times \frac{25°C}{18°C} = 71.7 \text{ lmh}$$

Sanitization and depyrogenation

Sanitization

For sanitization, thoroughly clean and rinse the membrane cartridges, then use any of the following:

- Up to 100 ppm* sodium hypochlorite. If properly cleaned, 10 ppm should be sufficient. Circulate 30 to 60 minutes.
- Up to 3% formalin. Circulate 30 to 60 minutes.
- Up to 0.5 N sodium hydroxide. Circulate 30 to 60 minutes at 50°C.
- 100 to 200 ppm peracetic acid. Circulate 30 to 60 minutes.
- Up to 70% ethanol in water.
- Autoclave.

*100 ppm active NaOCl = Household bleach diluted 250:1 with water

Be certain that the sanitizing solution makes continuous contact with all surfaces of concern.

Chemical sanitizing procedure

GE Healthcare hollow fiber cartridges can be chemically sanitized by following the steps below:

1. Thoroughly clean and rinse the cartridge.
2. Set up the separations system to recirculate the retentate and permeate back to the feed reservoir.
3. Prepare a sanitizing solution as noted previously and put a sufficient volume of the solution into the feed reservoir. Typically, the solution volume is 3 to 4 times the minimum working volume of the system.
4. Open the retentate and permeate valves. Start the feed pump on slow and increase the feed rate until solution flows from the retentate and permeate lines.
5. Adjust transmembrane pressure to:
   - 1 barg (15 psig) for 1,000 NMWC and 3,000 NMWC pore sizes
   - 0.7 barg (10 psig) for 5,000 NMWC through 50,000 NMWC pore sizes
   - 0.3 barg (5 psig) for larger ultrafiltration pore sizes and microfiltration membranes
6. Open the retentate valve and close the permeate valve until no bubbles appear in the permeate stream.
7. Open the permeate valve and, if necessary, adjust retentate valve to maintain transmembrane pressure noted in step 5, above.
8. Circulate the sanitization solution for 30 to 60 minutes for sanitization. Again, be certain that the solution makes contact with all surfaces of concern.
9. Flush the sanitizing solution from the cartridge using the new cartridge rinsing procedure. Note different pressures are used for ultrafiltration and microfiltration membranes. Flush until all traces of sanitizing solution are removed.

Depyrogenation

For depyrogenation, thoroughly clean, sanitize, and rinse the membrane cartridges, then recirculate either of the following solutions:

- 100 ppm sodium hypochlorite, pH 10 to 11 at 50°C
- 0.1 N to 0.5 N sodium hydroxide, pH 13 at 50°C

Depyrogenation procedure

Follow these steps to depyrogenate the cartridge:

1. Thoroughly clean and rinse the cartridge.
2. Recirculate depyrogenation solution for 30 to 60 minutes at 30°C to 50°C (86°F to 122°F).
3. Thoroughly drain the system.
4. Flush with non-pyrogenic water using the new cartridge rinsing procedure described previously.

Buffer conditioning

Before processing your sample, it is often helpful to precondition the filtration system with a buffer similar in pH and ionic strength to that of your sample. Conditioning the system removes trapped air and minimizes unwanted chemical reactions between your sample and the wetted parts of the filtration system. You can also use buffer conditioning to stabilize the system temperature.

Follow these steps to condition the system with buffer:

1. Set up your filtration system to recirculate the retentate and permeate back to the feed reservoir.
2. Prepare the buffer solution. The recommended volume of buffer solution is 5 to 10 l/m^2 of filter surface area (0.5 to 1.0 l/ft^2).
3. Bring the buffer to the proper temperature (if conditioning for temperature control) and add it to the feed reservoir.
4. Open the retentate and permeate valves. Start the feed pump on slow and increase the feed rate until solution flows from the retentate and permeate lines.
5. Adjust transmembrane pressure to:
   - 1 barg (15 psig) for 1,000 NMWC and 3,000 NMWC pore sizes
   - 0.7 barg (10 psig) for 5,000 NMWC through 50,000 NMWC pore sizes
   - 0.3 barg (5 psig) for larger ultrafiltration pore sizes and microfiltration membranes
6. Open the retentate valve and close the permeate valve. Increase the retentate flow rate to the recommended operating cross flow rate for the cartridge. Close the permeate valve and run until no bubbles appear in the permeate stream.
7. Open the permeate valve and, if necessary, adjust the retentate valve to maintain transmembrane pressures noted in step 5, above.
8. Circulate the buffer solution for 30 minutes to condition for pH and ionic stability. If conditioning for temperature control, continue circulating until the temperature of the system stabilizes.
9. Drain the buffer from the feed reservoir, leaving a small amount in the bottom of the reservoir so that no air can be introduced into the system during the addition of sample or process fluids. Keep buffer in the other parts of the system to prevent air entrainment.

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