The question of time for a filtration cycle is resolved by determining total volume versus time during a test run at pressures approximating normal operating conditions. Flow rate decreases with time as the media plugs or as the cake builds up. Plotting log total volume per unit area versus log time usually gives a straight line suitable for limited extrapolation (Fig. 7 -7). If the filter area of production equipment is fixed, the time to filter a given batch size may be estimated.

Alternately, the filter area required to complete the process within an allotted time period may be established.

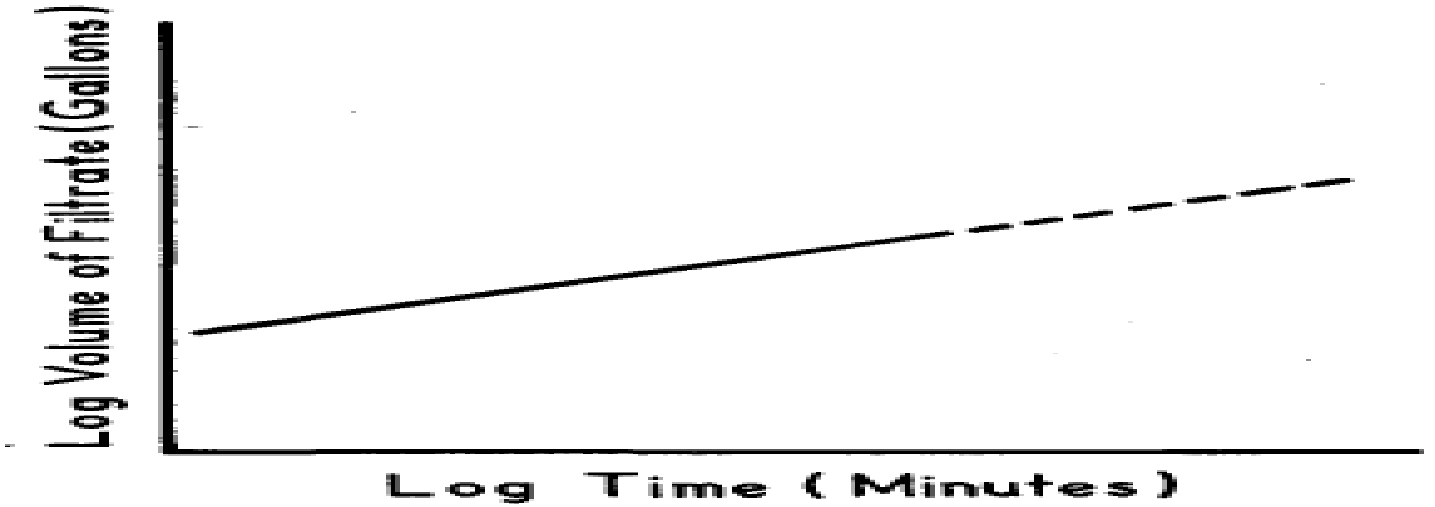


FIG. 7-7. *Extrapolation of filtrate volume produced in a given time can be made from log-log plots of experimental data.*

In semicontinuous operations, decisions must be made on length of the cycle prior to shutdown for replacement of media. If the goal is maximum output from the filter per unit of overall time, the graphic approach of Figure 7-8 is applicable.

During productive time T, the filter discharges a clear filtrate at a steadily decreasing rate. Nonproductive time T' is required to clean the filter and replace media. For graphic analysis, nonproductive time T' is plotted to the left of the origin of a volume V versus time curve. When a line is drawn from T' tangent to the curve, the value of V and T at the point of tangency indicates where the filtration should be stopped. The time lost in cleaning is offset by a return to high filtration rates associated with the new media.

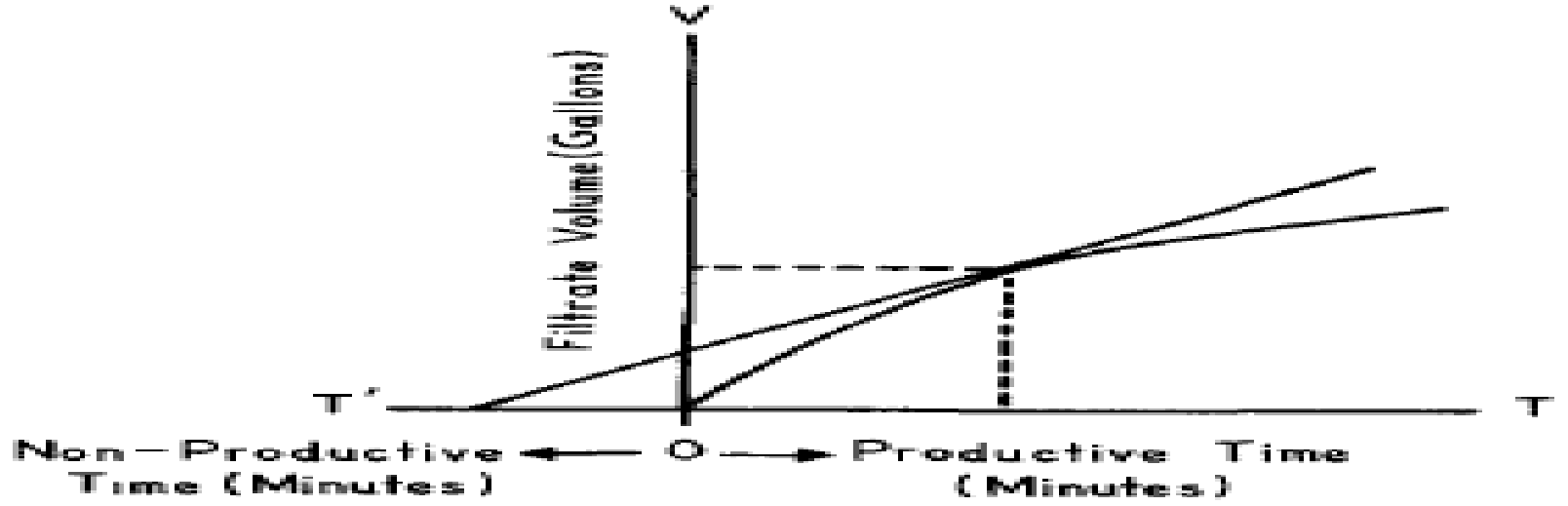


FIG. 7-8. *The optimal filtration cycle prior to cleaning can be determined by a graphic technique.*

Sterile Operations

Filtration may be used to clarify and sterilize pharmaceutical solutions that are heat labile. Until the introduction of membrane media, unglazed porcelain candles and the asbestos pad were the accepted standards.

The candle requires extensive cleaning and is a fragile medium.

High flow rates are attained only through use of multiple-element manifolds.

The asbestos pad has significant absorption and adsorption properties, and chemical prewash and pH adjustment are required to prevent interaction with products. Failure to achieve sterility may occur with asbestos pads owing to blow-through and channeling of medium of organisms when critical pressures are exceeded. Both asbestos and porcelain are migratory media; fragments of a candle or asbestos fibers may be found in the filtrate unless serial filtration through secondary media is used. Since membrane filters do not have these disadvantages, porcelain candles and asbestos pads are no longer considered media of choice for sterile filtration.

Membrane filters have become the basic tool in the preparation of sterile solutions and have been officially sanctioned by the United States Pharmacopoeia (USP) and the U.S. Food and Drug Administration (FDA). The available materials permit selection so that absorption effects are negligible and ionic or particulate contamination need not occur. The membrane requires no pretreatment and may be autoclaved or gas sterilized after assembly in its holder.

A sterility requirement imposes a severe restraint on filter selection. All sterility tests are presumptive, and one must rely upon total confidence in the basic process; economics becomes a secondary factor. Membranes with porosity ratings of 0.2 or 0.45 microns are usually specified for sterile filtrations. In this porosity range, membrane filters may clog rapidly, and a prefilter is used to remove some colloidal matter to extend the filtration cycle. The FDA allows the use of 0.45-micron filters only in cases of colloidal solutions in which 0.2-micron filters have been shown to clog very rapidly.

Most pharmaceutical liquids are compatible with one or more of the membrane filters now available. High viscosity or abnormal contaminant levels are the primary restraints to the use of membranes, since an extremely large filtration area is needed for practical flow rates. Oil and viscous aqueous menstruum are therefore heat-sterilized whenever possible. These solutions are usually clarified through coarser, nonsterilizing membranes, preferably prior to heat sterilization. Paraffin oils, however, may be successfully filtered through 0.2-micron membranes after heating to reduce viscosity. Simple formulations such as intravenous solutions, ophthalmics, and other aqueous products may be filtered directly through membranes in an economical manner.

Heat-labile oils and liquids containing proteins require pretreatment, e.g., centrifugation or conventional filtration, prior to sterilizing filtration. The objective is removal of gross contamination that would rapidly plug the finer membranes.

Difficult materials, such as blood fractions, demand serial filtration through successively finer membranes.

The cost of multiple filtration may seem excessive, but it is often the only way to achieve sterility.

Figure 7-9 illustrates the basic filtration system for nonsterile filtration of serum, water, and salts to reduce the microbiologic and particulate matter, followed by final filtration through the sterile membrane.

The use of filtration to remove bacteria, particulate matter from air, and other gases such as nitrogen and carbon dioxide is widespread in the pharmaceutical industry. The following are some common applications employing initial gas filtration:

Vent filtration

Compressed air used in sterilizers

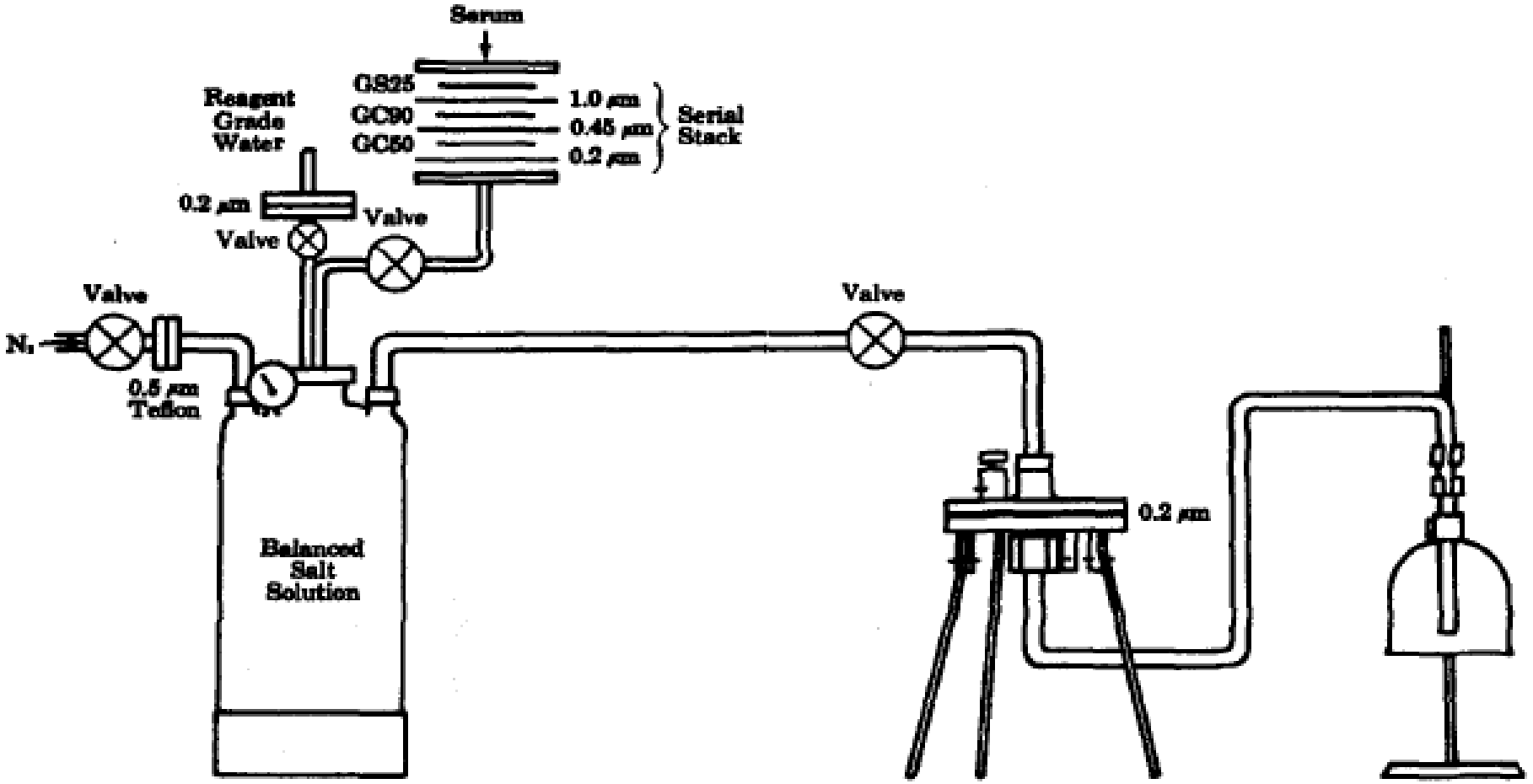
Air or nitrogen used for product and in-process solution transfers and at filling lines

Air or nitrogen used in fermentation

When sterile and under ideal conditions, traditionally packed fiberglass or cotton filters provide vent protection. The use of hydrophobic membrane filters is increasing. These filters guarantee bacterial removal in wet and dry air and do not channel, unload, or migrate the medium. These filters may need to be heated by jacketing. Restrictions of airflow through the vent filter can result in pump damage or tank collapse.

Non-Sterile Preparation in a Clean Room

Final Sterilizing Filtration in a Sterile Work Area



OBJECTIVE: Reduce Bioburden and Chemical Burden to Sterile Membrane

OBJECTIVE: Achieve Sterile Filtration

Manufacturers of membrane filters provide extensive application data and detailed directions for assembly, sterilization, and use of their filters. The basic elements of any sterile operation must be followed.

All apparatus should be cleaned and sterilized as a unit. Filtration should be the last step in processing, and the filter should be placed as close as possible to the point of use of final packaging. In serial filtrations, only the final unit need be sterile, but minimal contamination in prior steps increases the reliability of the total process. Sterile filtrations should always be a pressure operation; a vacuum is undesirable since bacteria may be drawn in at leaky joints and contaminate the product.

Integrity Testing

An important feature of a filtration system is its ability to be tested for integrity before and after each filtration. This is especially true in sterilization filtration, where even a few microorganisms passing through a crack in the filter could be disastrous.

An integrity test is a nondestructive test used to predict the functional performance of a filter. Each membrane has a characteristic bubble point, diffusion rate, or diffusion rate of air through water in a wetted filter, which is a function of the porosity rating and predicts the performance of the filter. The common integrity tests used to predict the performance of the filter are the bubble point test, the diffusion test, and the forward flow test.

Prior to filtration, the integrity test detects a damaged membrane, ineffective seals, or a system leak.

The test performed after filtration confirms that the filter is still intact and that the system is remaining leak-free throughout the run.

Bubble Point Test

Membrane filters, which have discrete uniform passages that penetrate from one side of the media to the other, can be regarded as fine, uniform capillaries.

The bubble point test is based on the fact that when these capillaries are full of liquid, the liquid is held by surface tension.

The minimum pressure *required to* force the liquid out of the capillary must be sufficient to overcome surface tension.

Figure 7-10 illustrates the principle in the bubble point test. As can be seen in this figure, the capillary pressure is higher in the case of a small pore than in that of a large pore. The same is true for pores in a membrane. The bubble point pressure is governed by the following equation:

$$P = K \frac{4\gamma \cos \theta}{D} \qquad (7)$$

ension in Capillary Tubes

where:

P = bubble point pressure
K = shape correction factor (experimental constant)
D = pore diameter
γ= surface tension of the liquid
θ= liquid-to-membrane contact angle (angle of wetting)

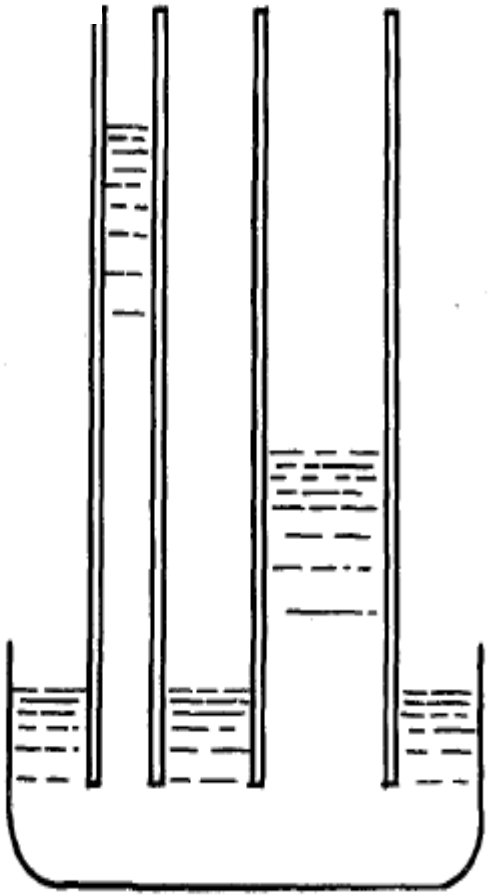


FIG. 7-10. *Surface tension in capillary tubes.*

In performing a bubble point experiment, the membrane is wetted and usually has a liquid above and a gas below. Since the pores are full of liquid, there is no passage of gas at zero pressure.

There is still no passage of gas if the pressure is increased slightly.

When the bubble point pressure is reached, a small bubble forms at the largest opening. As the pressure is further increased, rapid bubbling begins to occur.

Bubble point pressure for a given membrane is different for different liquids. This can be seen in equation (7), where the contact angle changes with different liquids.

Filtration should normally be performed at pressures lower than the bubble point of a membrane. This prevents gas from passing through the filter at the end of a filtration cycle and thereby prevents excessive foaming.

$$P = K \frac{4\gamma \cos \theta}{D} \qquad (7)$$

The bubble point is also a useful criterion for testing membrane efficiency. Figure 7-11 is a schematic diagram of a nondestructive test apparatus that may be used without loss of product or a break in sterility. A *bubble test* may be run during and after filtration as an in-process control.

After wetting the filter and venting the unit, valve A is closed, and air pressure is imposed on the filter through valves B and C. When valve C is closed, the filter holder should retain the pressure on the pressure gauge, and no bubbles should appear in the receiving vessel. Failure to hold a rated pressure is evidence of an unreliable membrane or improper holder assembly.

When such failure occurs, filtration should be discontinued, and material already processed should be refiltered. Although each membrane has a specific bubble point, which is dependent on the liquid wetting the membrane, a test at a pressure of 20 pounds per square inch (psi) is usually sufficient to detect leaks. Figure 7-12 illustrates the apparatus for performing a bubble point test on cartridge filters.

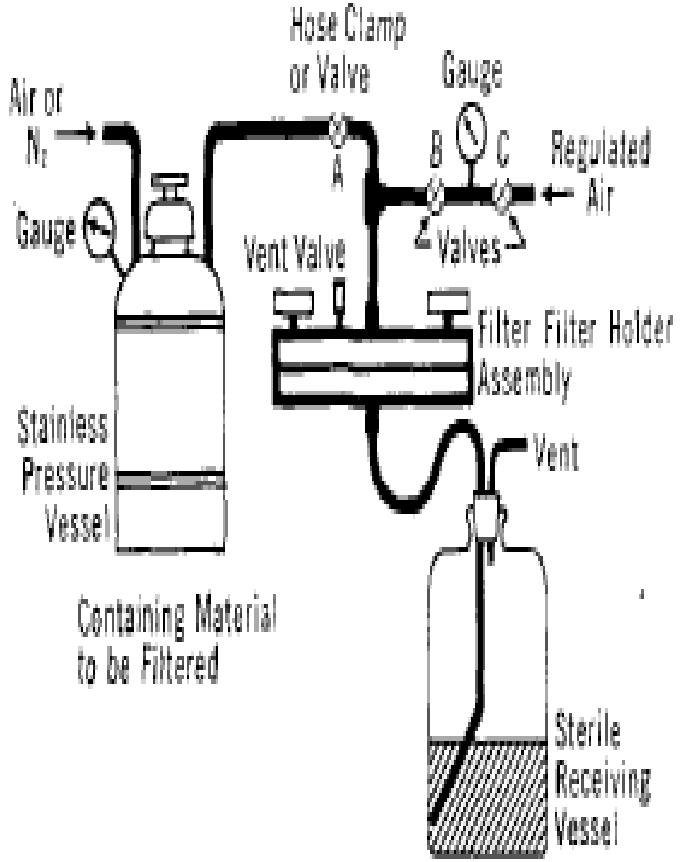


FIG. 7-11. *Connections for nondestructive bubble test to assure that membrane filter is intact. The test does not affect sterility. (Courtesy of Millipore Corporation)*

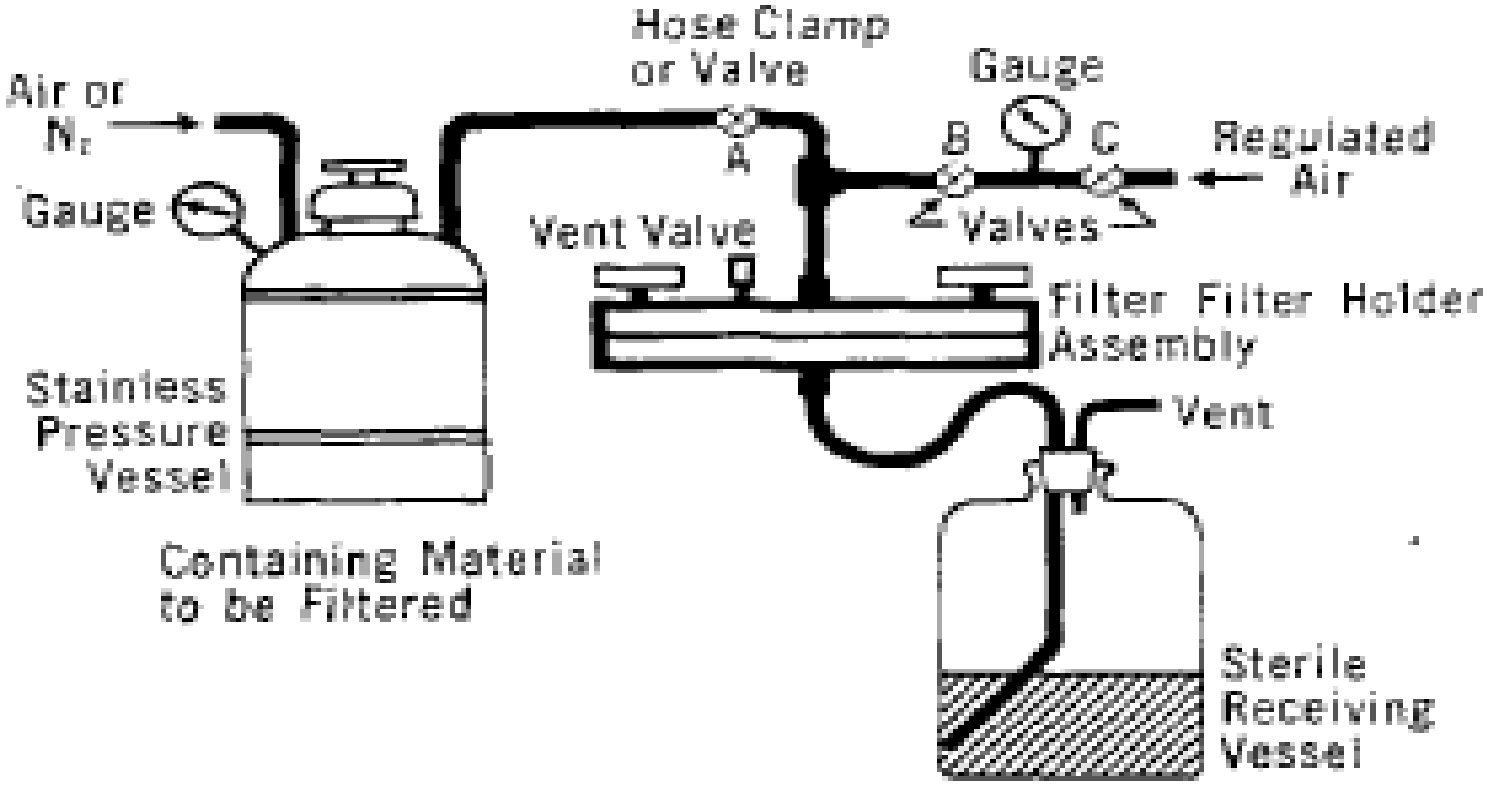


FIG. 7-11. *Connections for nondestructive bubble test to assure that membrane filter is intact. The test does not affect sterility. (Courtesy of Millipore Corporation)*

Diffusion Testing

A diffusion test must be performed in high volume systems, e.g., cartridges or multi stack discs, where a large volume of downstream liquid must be displaced before bubbles can be detected. A diffusion test measures volume of air that flows through a wet membrane from the pressurized side *to* the atmospheric side. The test is based on the theory that in a wet membrane filter: under pressure, air flows through the water-filled pores at differential pressures below the bubble point pressure of the filter by a diffusion process. The process follows Fick's law of diffusion. In performing the diffusion test the filter is thoroughly wetted in place with water, or the membrane is tested after filtration. Pressure is applied using air at 80% of the established bubble point pressure for the particular membrane. Pressure is held for 2 min, and the volume of the air displaced is recorded. The volume of air is determined by measuring the rate of flow of the displaced water.

The pressure is increased until the bubble point is reached at an increment of 2 psi. Applying pressure at 80% of the bubble point pressure validates filter integrity since there would be a significant increase in airflow (water flow) at lower pressures, indicating damaged membranes, wrong pore size filter, ineffective seals, system leaks, or a broad pore size distribution.

Forward Flow Test

Forward flow testing is based upon measurement of the diffusion rate of air through water in a wetted filter at a pressure well below the bubble point pressure. The following three kinds of tests can be performed, but often, only one or two are deemed sufficient.

1.Measurement of forward flow of individual elements prior to assembly to their housing to verify the integrity of each element prior to use.

2. Measurement of forward flow of the assembly with elements in place *in* the system, before or after autoclaving, by in situ steaming or by ethylene oxide to verify tightness of any valves in parallel with elements.

Measurement of forward flow of assembly after completion of the filtration procedure to verify the integrity of the element during filtration.

The test is performed by placing a given element in its holder and wetting the filter.

A preselected air pressure is applied to the upstream side of the filter system. Measurement of the total rate of airflow through the filter system is then made. The quality acceptance level for a given filter is based on a maximum total airflow at which the filter appears, empirically, to retain all bacteria.

Filtration Equipment and Systems

Commercial Equipment

Commercial filtration equipment is classified by type of driving force (gravity, pressure, centrifugal, or vacuum), by method of operating (batch or continuous), and by end product desired (filtrate of cake solids).

The clarification demands of pharmaceutical processes are usually met by batch pressure units. Compatibility with a wide range of products restricts materials of construction to stainless steel, glass, and inert polymers.

Gravity filters are common in water treatment, where a *sand filter* may be used to clarify water prior to deionization or distillation. The filtering medium may consist of sand or cake beds or for special purposes, a composition containing asbestos, cellulose fibers, activated charcoal diatomaceous earth, or other filter aids.

Small scale purification of water may use porous ceramics as a filter medium in the form of hollow "candles." The fluid passes from the outside through the porous ceramics into the interior of the hollow candles. *Tray and frame* filters are best adapted for slow, difficult filtrations and for exceptionally soft or fine grained precipitates, which clog under the slightest pressure or pass through the openings of a cloth.

***Gravity bag filters* also are applied to concentration of magmas, such as milk of magnesia. More efficient methods, however, particularly with respect to space requirements, are available. The *gravity nutzch* is a false-bottom tank or vessel with a support plate for filter media.**

Vacuum filters are employed on a large scale, but are rarely used for the collection of crystalline precipitates or sterile filtration. Continuous vacuum filters can handle high dirt loads, and on a volume basis, are cheap in terms of cost per gallon of filtered fluid. In the operation of the continuous drum filter system, vacuum is applied to the drum, and the fluid flows through the continuous belt. Solids are collected at the end of the belt.

Pressure filtration is desired in handling large quantities of material in order to accelerate the filtration process. Liquids with high viscosity can hardly be filtered at all by gravity. The *plate and frame filter press* is the simplest of all pressure filters and is the most widely used (Fig. 7-13). Filter presses are used for a high degree of clarification of the fluid and for the harvesting of the cake. When clarity is the main objective, a "batch" mode operation is applied.

The filter media are supported by structures in a pressure vessel. When an unacceptable pressure drop across the filter is reached during the filtration process, the filter media are changed.

Methods of supporting the filter media include horizontal plates, horizontal or vertical pressure leaf, and plate and frame.

As the name implies, the plate and frame filter press is an assembly of hollow frames and solid plates that support filter media. When assembled alternately into a horizontal or a vertical unit, conduits permit flow of the slurry into the frames and through the media. One side of the plate is designed for the flow of the feed. After passing the filter media, the filtrate is accommodated on the other side. The solids collect in the frames, and filtrate is removed through place conduits. In cake filtration, the size of the frame space is critical, and wide. sludge frames are used.

The filter press is the most versatile of filters since the number and type of filter sheets can be varied to suit a particular requirement. It can be used for coarse to fine filtrations, and by special conduit arrangements, for multistage filtration within a single press. The filter press is the most economical filter per unit of filtering surface, and material of construction can be chosen to suit any process conditions. Labor costs in assembly and cleaning are a primary disadvantage, and leakage between plates may occur through faulty assembly. The normal range of flow is three gallons per minute per square foot of filter surface at pressures of up to 25 psi.

The *disc filter* overcomes some deficiencies of the filter press (Fig. 7-14). Compactness, portability, and cleanliness are obvious advantages for pharmaceutical batch operations. The term disc filter is applied to assemblies of felt or paper discs sealed into a pressure case. The discs maybe preassembled into a self-supporting unit, or each disc may rest on an individual screen or plate. Single plate or multiples of single plates may be applied. The flow may be from the inside out or the outside in Figure 7-15 illustrates the flow schematics through a plate. Fluid flows from the outside along the thin flow channel in the plate.

The filtrate flows along similar channels in the bottom plate, and then to the inside circumference. This type of filter is intended only for clarification operations. Flow rates are similar to plate and frame presses at operating pressures of up to 50 psi. Pulp packs or *filtermasse* may be used instead of disc sheets for high-polish filtrations, but flow rates are then appreciably lower. Maximum filtrate recovery by air displacement of liquid is usually possible with a disc filter. Pressure leaf filters utilize the rotation of a pressure leaf to partially remove the cakes and extend the life of the filter media.

When filter aids are required, a plate and frame press with sludge frames is generally acceptable, but disposal of cake and cleaning becomes time-consuming. The *precoat pressure filter* (Fig. 7-15) is designed to overcome this objection. It consists of one or more leaves. plates, or tubes upon which a coat of filter aid is deposited to form the filtering surface. The filter area is usually enclosed within a horizontal or vertical tank, and special arrangements permit discharge of spent cake by backflush, air displacement, vibration, or centrifugal action. This type of filter is desirable for high-volume processes. Two or more units can be used alternatively, or surge tanks for clear filtrate may permit intermittent operation of a single unit.