7

Clarification and Filtration

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The preparation of pharmaceutical dosage forms frequently requires the separation of particles from a fluid. The usual objective is a sparkling liquid that is free of amorphous or crystalline precipitates, colloidal hazes, or insoluble liquid drops. Sterility specifications may expand the objective to include removal of microorganisms.

Filtration is defined as the process in which particles are separated from a liquid by passing the liquid through a permeable material. The porous filter medium is the permeable material that separates particles from the liquid passing through it and is known as a *filter*. Thus, filtration is a unit operation in which a mixture of solids and liquid, the *feed, suspension, dispersion, influent* or *slurry,* is forced through a porous medium, in which the solids are deposited or entrapped. The solids retained on a filter are known as the *residue*. The solids form a *cake* on the surface of the medium, and the clarified liquid known as *effluent* or *filtrate* is discharged from the filter. If recovery of solids is desired, the process is called *cake filtration*. The term *clarification* is applied when the solids do not exceed 1.0% and filtrate is the primary product. *Ultrafiltration* may be defined as the separation of intermicellar liquid from solids by the use of pressure on a semipermeable membrane.

Filtration is frequently the method of choice for sterilization of solutions that are chemically or physically unstable under heating conditions. In many applications, *sterile filtration* is an ideal technique. Sterile filtration of liquids and gases is commonly used in the pharmaceutical industry. Final product solutions or vehicles for suspensions are sterile-filtered prior to an aseptic filling process. Sterile filtration of bulk drug solution prior to an aseptic crystallization process eliminates the possibility of organisms being occluded within crystals.

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The broad span of pharmaceutical requirements cannot be met by a single type of filter. The industrial pharmacist must achieve a balance between filter media and equipment capabilities, slurry characteristics, and quality specifications for the final product. The choice is usually a batch pressure filter, which uses either surface or depth principles.

Surface filtration is a screening action by which pores or holes in the medium prevent the passage of solids. The *depth filter* permits slurry to penetrate to a point where the diameter of a solid particle is greater than the diameter of a tortuous void or channel. The solids are retained within a gradient density structure by physical restriction or by absorption properties of the medium.

Theory

Even today, filtration is more an art than a science. The filtration theory, with all its mathematical models, has a deficiency. The deficiency is its preoccupation with resistance to flow, almost to the exclusion of considerations of filtrate quality. It is possible to estimate the resistance to flow of a clean filter medium but impossible to estimate with comparable accuracy what the resistance will be as the filter begins to trap solids. The mathematical models do provide a means of showing apparent relationships between variables in a process and may be valuable decision-making tools in the selection of apparatus and techniques for a particular filtration application.[1]

The mathematical models for flow through a porous medium, cake filtration, and granular bed filtration may differ, but all follow this basic rule: The energy lost in filtration is proportional to the rate of flow per unit area.

The flow of liquid through a filter follows the basic rules that govern flow of any liquid

through a medium offering resistance. The rate of flow may be expressed as:

$$\text{rate} = \frac{\text{driving force}}{\text{resistance}} \quad (1)$$

The rate may be expressed as volume per unit time and the driving force as a pressure differential. The apparent complexity of the filtration equations arises from the expansion of the resistance term. Resistance is not constant since it increases as solids are deposited on the filter medium. An expression of this changing resistance involves a material balance as well as factors expressing permeability or coefficient of resistance of the continuously expanding cake.

The rate concept as expressed in modifications of Poiseuille's equation is prevalent in engineering literature:

$$\frac{dV}{dT} = \frac{AP}{\mu\,(\alpha W/A + R)} \quad (2)$$

where:

V = volume of filtrate
T = time
A = filter area
P = total pressure drop through cake and filter medium
μ = filtrate viscosity
α = average specific cake resistance
W = weight of dry cake solids
R = resistance of filter medium and filter

Any convenient units may be used in this equation, since inconsistencies are absorbed in the cake and filter resistances.

The practical limitation of this equation is that the constants must be determined on the actual slurry being handled. There is no crossover application of data, and the majority of filters are selected on the basis of empiric laboratory or pilot plant tests. Equation (2) has been integrated under various assumptions, and these integrated forms may be used to predict effects of process changes and to evaluate test work. The techniques for data evaluation set forth in the section "Filter Selection" in this chapter may be confirmed by reference to broader theoretic discussions.[2–4]

Interpretation of the basic equation, however, leads to a general set of rules:

1. Pressure increases usually cause a proportionate increase in flow unless the cake is highly compressible. Pressure increases on highly compressible, flocculent, or slimy precipitates may decrease or terminate flow.
2. An increase in area increases flow and life proportional to the square of the area since cake thickness, and thus resistance, are also reduced.
3. The filtrate flow rate at any instant is inversely proportional to viscosity.
4. Cake resistance is a function of cake thickness; therefore, the average flow rate is inversely proportional to the amount of cake deposited.
5. Particle size of the cake solids affects flow through effect on the specific cake resistance, α. A decreased particle size results in higher values of α and proportionally lower filtration rates.
6. The filter medium resistance, R, usually negligible or about 0.1 α in cake filtration, is the primary resistance in clarification filtration. In the latter case, flow rate is inversely proportional to R.

It is convenient to summarize the theoretic relationship as:

$$\text{Rate of filtration} = \frac{(\text{area of filter}) \times (\text{pressure difference})}{(\text{viscosity}) \times (\text{resistance of cake and filter})} \quad (3)$$

Most clarification problems can be resolved empirically by varying one or more of these factors. A broader understanding of filtration theory is required only if cake filtration applications are under consideration.

The membrane filters are highly porous. A number of methods are used for establishing the pore size and pore size distribution. Most methods are derived from the interfacial tension phenomenon of liquids in contact with the filter structure. Each pore in the filter acts as a capillary. For a nonwetting fluid, the following equation was established by Poiseuille:[5]

$$p = \frac{-2\gamma \cos \theta}{r} \quad (4)$$

where:

p = applied pressure
γ = liquid surface tension
θ = contact angle between liquid and solid
r = radius of the pore

Filter Media

The surface upon which solids are deposited in a filter is called the *filter medium.*[6,7] For the pharmacist selecting this important element, the wide range of available materials may be bewildering. The selection is frequently based on past experience, and reliance on technical services of commercial suppliers is often advisable.

A medium for cake filtration must retain the solids without plugging and without excessive bleeding of particles at the start of the filtration. In clarification applications, in which no appreciable cake is developed, the medium is the primary factor in achieving clarity, and the choice is limited to materials that will remove all particles above a desired size. Sterile filtration imposes a special requirement, since the pore size must not exceed the dimension of microorganisms unless the filter is adsorptive, and since the medium should be sterilizable.

Filter media are available in different materials and forms. The filter fabrics are commonly woven from natural fibers such as cotton and from synthetic fibers and glass. The properties of these fibers and glass applicable for media selection are tabulated in Table 7-1.

Filter cloth, a surface type medium, is woven from either natural or synthetic fiber or metal. Cotton fabric is most common and is widely used as a primary medium, as backing for paper or felts in plate and frame filters, and as fabricated bags for coarse straining. Nylon is often superior for pharmaceutical use, since it is unaffected by mold, fungus, or bacteria, provides an extremely smooth surface for good cake discharge, and has negligible absorption properties. Both cotton and nylon are suitable for coarse straining in aseptic filtrations, since they can be sterilized by autoclaving. Monofilament nylon cloth is extremely strong and is available for openings as small as 10 microns. Teflon is superior for most liquid filtration, as it is almost chemically inert, provides sufficient strength, and can withstand elevated temperatures.

Woven wire cloth, particularly stainless steel, is durable, resistant to plugging, and easily cleaned. Metallic filter media provide good surfaces for cake filtrations and usually are used with filter aids. As support elements for disposable media, wire screens are particularly suitable, since they may be cleaned rapidly and returned to service. Wire mesh filters also are installed in filling lines of packaging equipment. Their function at this point is not clarification, but security against the presence of large foreign particles.

Nonwoven filter media include felts, bonded fabrics, and kraft papers. A *felt* is a fibrous mass that is free from bonding agents and mechanically interlocked to yield specific pore diameters that have controlled particle retention. High flow rate with low pressure drop is a primary characteristic. Felts of natural or synthetic material function as depth media and are recommended where gelatinous solutions or fine particulate matter are involved. *Bonded fabrics* are made by binding textile fibers with resins, solvents, and plasticizers. These materials have not

TABLE 7-1. *Fiber Properties For Filter Media Selection*

Fiber	*Temperature Recommended Safe Limit (°F)*	*Wet Breaking Tenacity (g/denier)*	*Acid Resistance*	*Alkali Resistance*	*Price Ratio to Cotton*
Cotton	210	3.3 6.4	Poor	Fair	1
Polyester (Dacron)	300	6.0 8.2	Very good	Good	2.7
Dynel modacrylic	200	3.0	Excellent	Excellent	3.2
Glass (spun)	750	3.0 4.6	Excellent	Fair	6.0
Glass (continuous filament)	550	3.9 4.7	Excellent	Fair	2.2
Nylon	250	2.1 8.0	Fair	Excellent	2.5
Acrylic (Orlon)	300	1.8 2.1	Excellent	Fair	2.7
Polyethylene	165	1.0 3.0	Excellent	Excellent	2
Polypropylene	175	3.5 8.0	Excellent	Excellent	1.75
Saran	160	1.2 2.3	Excellent	Excellent	2.5
Teflon	475	1.9	Excellent	Excellent	25.0
Polyvinylchloride	165	1.0 3.0	Good	Excellent	2.7
Wool	210	0.76 1.6	Very good	Fair	3.7
Rayon and acetate	210	1.9 3.9	Poor	Fair	1

found wide acceptance in dosage form production because of interactions with the additives. *Kraft* paper is a pharmaceutical standard. Although limited to use in plate and frame filters and horizontal-plate filters, it offers controlled porosity, limited absorption characteristic, and a low cost. The latter is important since concern over cross-contamination makes a disposable medium attractive to pharmacy. White papers are preferred, and they may be crinkled to produce greater filtration area. A support of cloth or wire mesh is necessary in large filter presses to prevent rupture of the paper with pressure.

Porous stainless steel filters are widely used for removal of small amounts of unwanted solids from liquids (clarification) such as milk, syrup, sulfuric acid, and hot caustic soda. Porous metallic filters can be easily cleaned and repeatedly sterilized.

Membrane filter media are the basic tools for microfiltration and ultrafiltration. They are used commonly in the preparation of sterile solutions. Membrane filters classified as surface or screen filters are made of various esters of cellulose or from nylon, Teflon, polyvinyl chloride, polyamide, polysulfone, or silver. The filter is a thin membrane, about 150 microns thick, with 400 to 500 million pores per square centimeter of filter surface. The pores are extremely uniform in size and occupy about 80% of filter volume. This high porosity permits flow rates at least 40 times faster than those obtained through other media of comparable particle retention capability.

Because of surface screening characteristics, prefiltration is often required to avoid rapid clogging of a membrane. The selection of a membrane filter for a particular application is a function of the size of the particle or particles to be removed. An approximate pore size reference guide can be set down as follows:

Pore Size (micron)	*Particle Removed*
0.2 (0.22)	All bacteria
0.45	All coliform group bacteria
0.8	All airborne particles
1.2	All nonliving particles considered dangerous in i.v. fluids
5	All significant cells from body fluids

The fragility of membrane filters is partially overcome by the use of monofilament nylon as a supporting web within the membrane structure.

The distinction between ultrafiltration and microfiltration lies in the nature of the filter medium. Ultrafiltration membranes contain pores of relatively narrow size distribution 10^{-3} to 10^{-2} microns (10 to 100 Å) and are formed by etching cylindric pores into a solid matrix. Ultrafiltration membranes are fragile and require supporting substrates because of the high-pressured differences required during filtration.

Most types of filter media are also available as *cartridge units*. These cartridges are economical and convenient when used to remove low percentages of solids ranging in particle size from 100 microns to less than 0.2 micron. The cartridge may be a surface or depth filter and consists of a porous medium integral with plastic or metal structural hardware. Synthetic and natural fibers, cellulose esters and fiberglass, fluorinated hydrocarbon polymers, nylon, and ceramics are employed for the manufacture of disposable cartridges. Porous materials for cleanable and reusable cartridges use stainless steel, Monel, ceramics, fluorinated hydrocarbon polymers, and exotic metals.

Surface-type cartridges of corrugated, resin-treated paper are common in hydraulic lines of processing equipment, but are rarely applied to finished products. Ceramic cartridges have the advantage of being cleanable for reuse by backflushing, and porcelain filter candles are acceptable for some sterile filtrations along with membrane filters in cartridge form. Sintered metal or woven-wire elements are also useful, but fine-wire mesh lacks strength. The metallic-edge filters overcome this problem by allowing liquid to pass between rugged metal strips, which are separated by spacers of predetermined thickness. *Depth-type cartridges* consist of fibrous media, usually cotton, asbestos, or cellulose. The cartridge may be formed by felting or by resin-bonding fibers about a mandrel. Effective units are also manufactured by winding yarn around a central supporting screen. The depth cartridge is always a disposable item since cleaning is not feasible.

Filter Aids

Justification for use of filter aids may be found in equation (2), which shows the rate of filtration to be inversely proportional to the resistance of the solids cake. Therefore, the pressure drop across the system is directly proportional to the filtration rate, the thickness of the cake, and the liquid viscosity for flow through porous media, when laminar flow conditions exist in the filter media or cake. It is also inversely proportional to the density of the liquid and square of the particle diameter. Poorly flocculated solids offer higher resistance than do flocculated solids or solids providing high porosity to the cake. In the case of cake filtration, the rate varies with the

square of the volume of liquid. When the volume of the filter cake solids per unit volume of filtrate is low, the solids formed on the filter medium may penetrate the voidspace, thus making the filter medium more resistant to flow. At a higher concentration of solids in a suspension, the bridging over of openings over the voidspace, rather than blinding of the openings, seems to predominate. Slimy or gelatinous materials, or highly compressible substances, form impermeable cakes with high resistance to liquid flow. The filter medium becomes plugged or slimy with accumulation of solids, and the flow of filtrate stops. A filter aid acts by reducing this resistance.[8,9]

Filter aids are a special type of filter medium. Ideally, the filter aid forms a fine surface deposit that screens out all solids, preventing them from contacting and plugging the supporting filter medium. Usually, the filter aid acts by forming a highly porous and noncompressible cake that retains solids, as does any depth filter. The duration of a filtration cycle and the clarity attained can be controlled as density, type, particle size, and quantity of the filter aid are varied. The quantity of the filter aid greatly influences the filtration rate. If too little filter aid is used, the resistance offered by the filter cake is greater than if no filter aid is used, because of added thickness to the cake. On the other hand, if high amounts of filter aid are added, the filter aid merely adds to the thickness of the cake without providing additional cake porosity. Figure 7-1 is a typical plot of filter aid concentration versus permeability. In the figure, flow rate and permeability are directly proportional to each other. At low concentrations of filter aid, the flow rate is slow because of low permeability. As the filter aid concentration increases, the flow rate increases and peaks off. Beyond this point, the flow rate decreases as the filter aid concentration is increased.

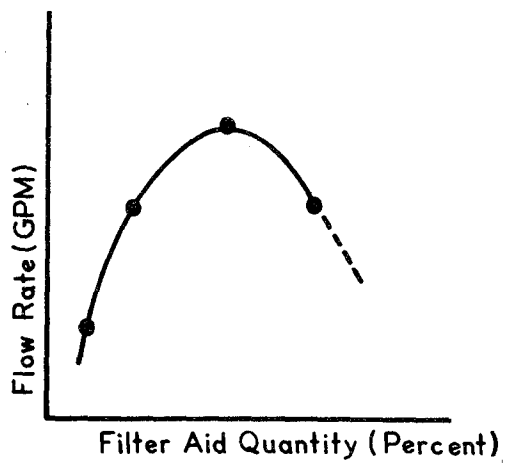


FIG. 7-1. *Experimental determination of flow rate as a function of filter aid quantity discloses correct operating level.*

The ideal filter aid performs its functions physically or mechanically; no absorption or chemical action is involved in most cases. The important characteristics for filter aids are the following:[10]

1. It should have a structure that permits formation of pervious cake.
2. It should have a particle size distribution suitable for the retention of solids, as required.
3. It should be able to remain suspended in the liquid.
4. It should be free of impurities.
5. It should be inert to the liquid being filtered.
6. It should be free from moisture in cases where the addition of moisture to the fluid would be undesirable.

The particles must be inert, insoluble, incompressible, and irregularly shaped. Filter aids are classified from low flow rate (fine: mean size in the range of 3 to 6 microns) to fast flow rate (coarse: mean size in the range of 20 to 40 microns). Clarity of the filtrate is inversely proportional to the flow rate, and selection requires a balance between these factors. Filter aids are considered to be equivalent in performance when they produce the same flow rate and filtered solution clarity under the same operating conditions when filtering a standard sugar solution.[1] Table 7-2 lists the advantages and disadvantages of filter aid material.

Diatomite (diatomaceous earth) is the most important filter aid. Processed from fossilized diatoms, it has an irregularly shaped porous particle that forms a rigid incompressible cake. Since diatomite is primarily silica, it is relatively inert and insoluble. *Perlite,* an aluminum silicate, forms filter cakes that are 20 to 30% less dense than diatomic cakes. Perlite is not a porous incompressible particle, but it has an economic advantage over diatomite.

Cellulose, asbestos, and *carbon* filter aids are also commercially available. Cellulose is highly compressible and costs two to four times more than diatomite or perlite. It is reserved for applications where the liquids may be incompatible with silica compounds. Cellulose is used as a

TABLE 7-2. *The Advantages and Disadvantages of Filter Aid Materials*

Material	*Chemical Composition*	*Advantages*	*Disadvantages*
Diatomaceous earth	Silica	Wide size range available; fines reduced by calcination; can be used for very fine filtration.	Slightly soluble in dilute acids and alkalies.
Expanded perlite	Silica and aluminosilicates	Wide size range available; not capable of finest retention of diatomites.	More soluble than diatomites in acids and alkalies; may give highly compressible cakes.
Asbestos	Aluminosilicate	Usually used in conjunction with diatomites; very good retention on coarse screens.	Chemical properties similar to perlite.
Cellulose	Cellulose	Used mainly as a coarse precoat; high purity; excellent chemical resistance—slightly soluble in dilute and strong alkalies, none in dilute acids.	Expensive
Carbon	Carbon	May be used for filtering strong alkaline solutions	Available in coarser grades only; expensive

Reprinted from Akers, R., and Ward, A.: Liquid filtration theory and filtration treatment. *In* Filtration Principles and Practices, Part I. Edited by C. Orr. Marcel Dekker, Inc., New York, 1977, p. 237, by courtesy of Marcel Dekker, Inc.

coarse precoat. It is available in high-purity material and has excellent chemical resistance. Asbestos has good retention on coarse screens, but has limited application because of high cost, and because of concern over its toxicity should the fibers carry over into the filtrate. Asbestos filters may be used in pharmaceutical industry if their application is followed by a membrane filter. Nonactivated carbons that are not suitable for decolorization or absorption are rarely used in pharmaceutical applications because of cleanliness problems. They may be used for filtering strong alkaline solutions. Commercial blends of various filter aids are common, and these specialities, particularly those intended as water scavengers in oil filtrations, must be considered in selection of a filter aid.

Filter aids may be applied by *precoating* or *body-mix* techniques.[8,9] Precoating requires suspending the filter aid in a liquid and recirculating the slurry until the filter aid is uniformly deposited on the filter septum. The quantity varies from 5 to 15 pounds per 100 square feet of filter area, or that sufficient to deposit a cake 1/16 to 1/8 inches thick. The liquid is preferably a portion of the feed or retained filtrate from a prior cycle, since the physical properties of the precoat liquid must approximate those of the material to be filtered. Precoating should proceed at the same flow rates and pressures to be used in final filtration, and the transition from precoat liquid to regular feed must be rapid to prevent disruption of the cake. Body mix (direct addition of filter aid to the filter feed) is more common in batch pharmaceutical operations. The filter aid, 1 to 2 pounds per pound of contaminant, or 0.1 to 0.5% of total batch weight, is mixed into the feed tank. This slurry is recirculated through the filter until a clear filtrate is obtained; filtration then proceeds to completion. The body-mix method minimizes equipment requirements and cross-contamination potentials.

Often, a filter aid may be used that performs its function not physically or mechanically, but chemically, by reacting with the solids. These chemicals may cause the solids depositing in a filter bed to adhere more strongly to the filter medium. Water-soluble polymers such as flocculating agents are often used as filter aids. The polymers may be derived from vegetable or animal sources, or they may be produced synthetically. Compounds produced by modification of the chemical structure, such as starch, may be filter aids to more costly synthetic materials. Water-soluble polymers may be classified as nonionic, anionic, or cationic, depending on their property to ionize in water. There are a few commercially available water-soluble cationic polymers. These include acrylamide copolymers, polyethyleneimine, and derivatives of casein, starch, and guar gum.[1]

Filter aids are chosen by trial and error in either laboratory or plant. Within ranges previ-

ously indicated, the filter aid is usually selected to give acceptable filtrate at the highest flow rate; however, in pharmaceutical operations in which quality is a primary consideration, the selection usually favors the fine grades, which yield low flow rates. The most important pharmaceutical factor is inertness. A filter aid may have such extensive absorption properties that desired colored substances and active principles are frequently removed. The total quantity of any ingredient absorbed may be small, but it may be a considerable portion of the original concentration.

Filtration efficiency also may be affected by changes in temperature, since there is an inverse relationship of flow rate to viscosity. The viscosities of most liquids decrease with increase in temperature. According to the "hole theory," there are vacancies in a liquid, and there is a continuous movement of the molecules into these vacancies, thus causing vacancies to move around. This movement of vacancies permits flow, but requires energy. This energy is the activation energy with which a molecule has to move into a vacancy. The activation energy is more readily available at higher temperatures than at lower temperatures. Thus, the liquid can flow more easily at higher temperatures than at lower temperatures.[11] Table 7-3 lists the viscosities of some common liquids at different temperatures. Equation (5) represents the relationship of the coefficient of viscosity to temperature.

$$\eta = Ae^{E/RT} \qquad (5)$$

where:

η = coefficient of viscosity of the liquid
E = activation energy
R = ideal gas constant
T = absolute temperature
A = pre-exponential factor

According to the "hole theory," the viscosity of a liquid increases as the pressure is increased. Since the number of holes is reduced, it is more difficult for molecules to move around. Increasing the temperature of heavy pharmaceutical syrups lowers the viscosity and increases filtration rates. Most liquids must be maintained at a high temperature during filtration to prevent the formation of crystals. The filtration of cosmetic products at low temperatures, approximately 5°C, is also common. The consequent reduction in flow rate is tolerated, since the goal is reduced solubility of contaminants or perfume oils, resulting in their more effective removal. Filtration at room temperature would yield a liquid that might cloud at the lower temperatures encountered by the product under field conditions.

TABLE 7-3. *Viscosity of Liquids in Centipoise*

Liquid	*Temperature (°C)*			
	0	*25*	*50*	*75*
Water	1.793	0.895	0.549	0.380
Ethanol	1.79	1.09	0.698	—
Benzene	0.9	0.61	0.44	—

From Daniels, F., and Alberty, R. A.: Irreversible processes in solution. In Physical Chemistry. 3rd Ed. Edited by F. Daniels and R.A. Alberty. John Wiley and Sons, New York, 1966.

Filter Selection

In designing or selecting a system for filtration, the specific requirements of the filtration problem must be defined. The following questions should be answered before any assistance is requested from the manufacturers of filtration equipment.[12,13]

1. What is to be filtered—liquid or gas?
2. What liquid or gas is to be filtered?
3. What is the pore size required to remove the smallest particle?
4. What is the desired flow rate?
5. What will the operating pressure be?
6. What are the inlet and outlet plumbing connections?
7. What is the operating temperature?
8. Can the liquid to be filtered withstand the special temperature required?
9. What is the intended process—clarification or filtration?
10. Will the process be a sterilizing filtration?
11. Will the process be a continuous or batch filtration?
12. What is the volume to be filtered?
13. What time constraints will be imposed, if any?

Once the purpose of the process has been determined, the selection of the filter medium can be made. For example, for a sterilizing filtration, a 0.2-micron pore size is used; for clarification, a plate and frame filter or woven-fiber filter may be used. In general, a pore size smaller than the

smallest particle to be removed is selected. The filter medium should be compatible with the liquid or gas to be filtered. It is advisable to check the chemical compatibility charts provided by the vendors for selection of filter type. Filter type, cellulose, polytetrafluoroethylene (PTFE), fiber, metal, polyvinylidene difluoride, nylon, or polysulfones may be selected based on the chemical resistance to the most aggressive ingredient in the liquid. For vent filters or gaseous filtration, a hydrophobic filter medium should be chosen.

Filtration surface area is calculated after the filter media, pore size, required flow rate, and pressure differentials are established. For a liquid having a viscosity significantly different from that of water (1 cp), the clean water flow rate is divided by the viscosity of the liquid in centipoises to obtain the approximate initial flow rate for the liquid in question. For gaseous filtration at elevated temperature and exit pressures, the standard flow rate (20°C, 1 atmosphere) must be corrected by equation (6), the *gaseous filtration flow rate formula:*

$$F = F_0\left(\frac{293}{273 + t}\right)\left(\frac{P + \Delta P/2}{14.7 + \Delta P/2}\right) \qquad (6)$$

where:

F = corrected flow rate
F_0 = standard flow rate from chart (20°C, 1 atmosphere)
t = temperature of air or gas (°C)
P = exit pressure (psia)
ΔP = pressure drop through the system (psi)

If the pressures are expressed in kg/cm^2, the term 14.7 in equation (6) becomes 1.03.

The optimum system often requires use of a series of filters in a single multilayered filter containing layers of various pore sizes or a prefilter followed by a final filter. Optimum performance is obtained when the filters in a series exhaust their dirt-holding capacities at the same time. When the flow resistance across each filter in the series approaches the limiting pressure drop, the dirt-holding capacity of the system is considered expended. Figures 7-2 through 7-5 illustrate the prefilters with adequate and inadequate dirt holding capacity. In Figure 7-3, the coarse prefilter does not provide sufficient retention efficiency, thus causing the poorly protected final filter to clog prematurely. Too fine a filter, on the other hand, has enough retention efficiency but insufficient dirt-holding capacity, and it plugs very quickly, as illustrated in Figure 7-4. As shown in Figure 7-5, both filters—the

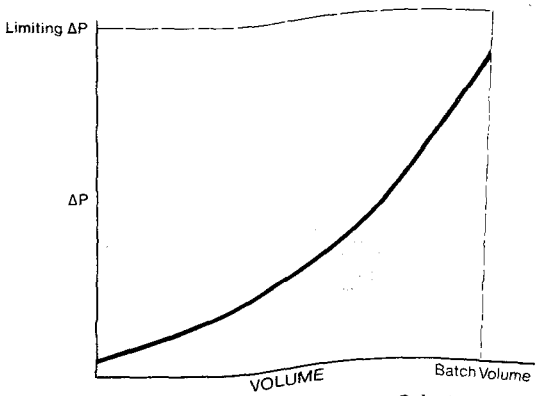


FIG. 7-2. *Ideal filtration system. (From Cole, J. C., and Shumsky, R.: Pharm. Tech., 1:39, 1977.)*

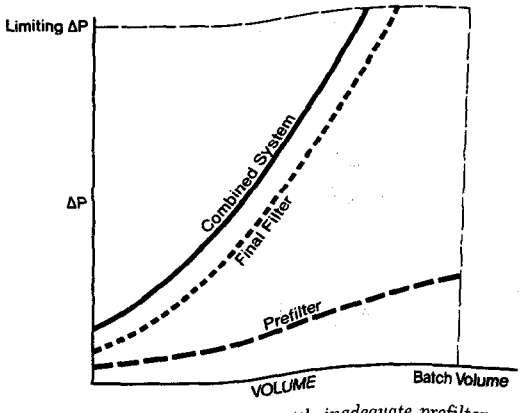


FIG. 7-3. *Filtration system with inadequate prefilter—too coarse. (From Cole, J. C., and Shumsky, R.: Pharm. Tech., 1:39, 1977.)*

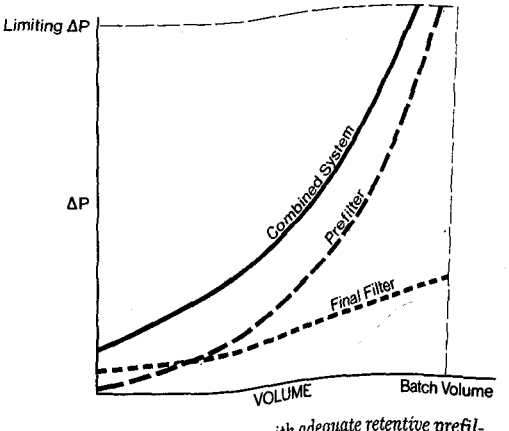


FIG. 7-4. *Filtration system with adequate retentive prefilter but inadequate dirt-holding capacity. (From Cole, J. C., and Shumsky, R.: Pharm. Tech., 1:39, 1977.)*

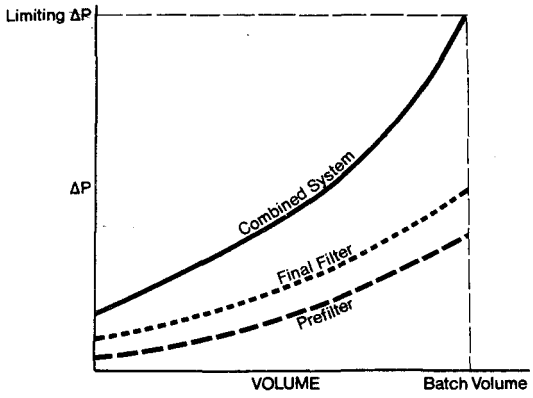


FIG. 7-5. *Filtration system with adequate prefilter. (From Cole, J. C., and Shumsky, R.: Pharm. Tech., 1:39, 1977.)*

final filter and the "correct" prefilter—will have almost expended their dirt-holding capacities as the last of the batch is filtered. A final filter that is not protected by prefilter has a short filter life. When a prefilter is used in combination with a final filter, the efficiency of the prefilter is maximum. In these cases, it is important that the O-ring seal sits directly on the membrane itself and not on the prefilter. Therefore, the diameter of the disc prefilter selected should be somewhat smaller than the diameter of the final filter. Table 7-4 lists the diameter of the filter and the diameter of the prefilter when used in combination. Seating the O-ring on the prefilter often fails to produce a seal, thus causing the filtration system to leak. This leakage may result in the filtrate being exposed to contamination.

Nonsterile Operations

Although filtration analysis can be sophisticated, pilot plant studies are usually basic. The common problems are to select the media, determine the time required, and if possible, estimate when a semicontinuous cycle should be terminated for cleaning.

For nonsterile polish filtrations, the quality level must be established prior to choice of media. Particulate matter above 30- to 40-micron particles may be noticeable. Most pharmaceutical filtrations therefore aim for removal of particles of 3 to 5 microns or less. A nephelometer, an instrument that measures the degree of light scattering (Tyndall effect) in dilute suspensions, is an excellent tool for assessing effectiveness in this range.

The nephelometer gives a quantitative value to the formulator's quality specification of "sparkling clear." This value may be used to compare results using different filtration media. Figure 7-6 shows a typical curve obtained from filtration of an elixir through disposable cartridges and standard kraft paper. If an existing process is to be shifted from paper on a filter press to cartridges, this curve permits selection of an element that gives comparable performance. The technique also may be applied to assessment of filter aid effectiveness by determining transmittance as a function of filter-aid type, quantity, or method of use.

In addition to improving clarity, filter aids are used to increase flow rates. Figure 7-1 indicates a typical flow rate pattern as the amount of filter aid is increased. Exceeding an optimum quantity can frequently lead to decreased flow rate without improving clarity. The filter aid quantity can be expressed as a percentage of cake solids, a percentage of filter aid in body mix, or the weight applied as a precoat per unit of filter area.

TABLE 7-4. *Diameter of Filter and Corresponding Prefilter When Used in Combination*

Filter Size (mm)	*Prefilter Size (mm)*
25	22
47	35
90	75
142	124
293	257

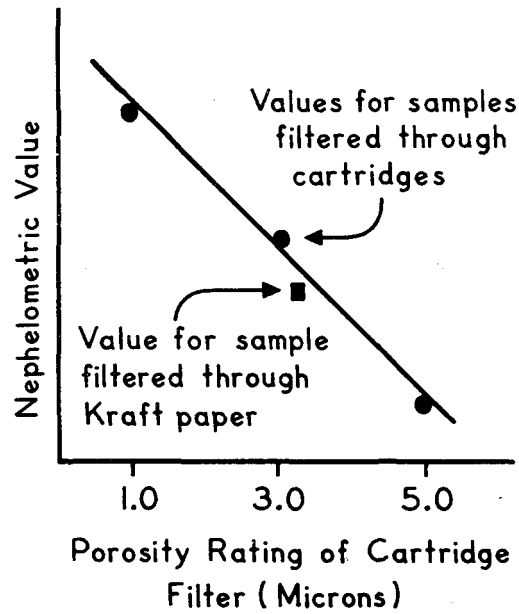


FIG. 7-6. *A nephelometer reading of a filtrate provides data that may be used to compare performance of different media.*

Flow rate should be determined for each case at constant pressure and after a uniform time interval. The maximum filter aid level used in laboratory tests must be within the cake capacity of projected or existing plant equipment.

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. Similar flow decay studies can also be performed during sizing of a filtration system for sterile operations.

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

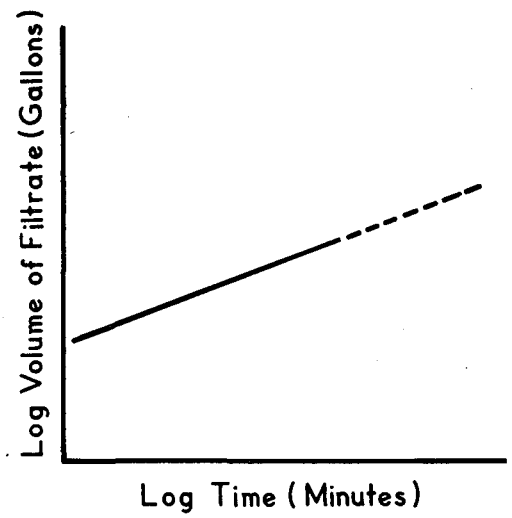


FIG. 7-7. *Extrapolation of filtrate volume produced in a given time can be made from log-log plots of experimental data.*

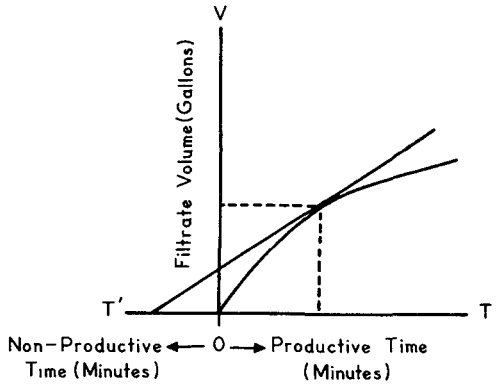


FIG. 7-8. *The optimal filtration cycle prior to cleaning can be determined by a graphic technique.*

stopped. The time lost in cleaning is offset by a return to high filtration rates associated with the new media. This point also can be calculated from theoretic relationships for constant pressure or constant volume filtration.[14] Data from laboratory equipment can be applied to production units since the analysis is independent of filter area.

The evaluation of coarse straining operations is limited to sizing a filter that will not have excessive pressure drop. The amount of impurity is usually small, and continued operation does not significantly decrease filter capacity. The metal cartridge filters, either woven-mesh or edge-type, and porous sintered stainless steel, have replaced cheesecloth in most pharmaceutical applications. Straining suspensions containing gums or other viscous ingredients can be accomplished with self-cleaning edge filters. These suspensions frequently bridge the media, and cleaning devices are needed to maintain adequate flow.

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 menstruums 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.[15]

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.

In selecting a filtration system for sterilization of any growth-supporting medium, the following precautions must be kept in mind:

1. Identify the potential sources of adverse biochemical and chemical contamination at each point of the system.
2. Identify the control points necessary to eliminate possible contamination and decrease cost.
3. Identify the hazards associated with each control point, i.e., airborne contamination and protein denaturation.
4. Establish a protocol for monitoring the hazards at control points of the system.

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.[13]

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.[16] 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.[17]

Manufacturers of membrane filters provide extensive application data and detailed directions for assembly, sterilization, and use of their filters.[12,13,18–31] 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 filtra-

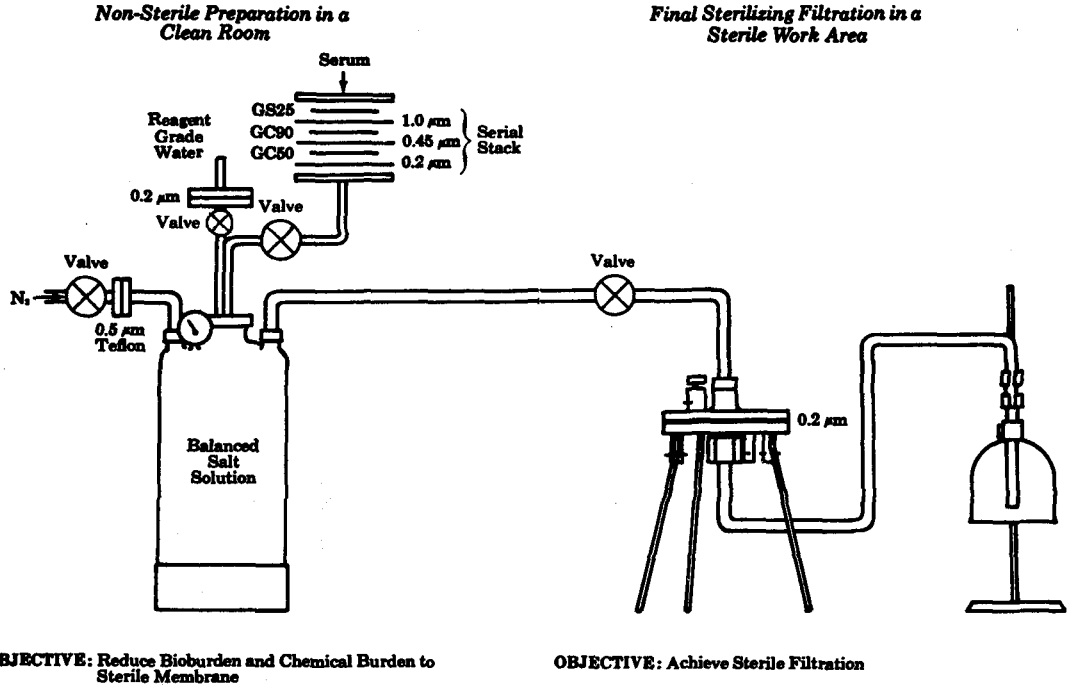


FIG. 7-9. *Schematic representation of operational sequence.*

tions should always be a pressure operation; a vacuum is undesirable since bacteria may be drawn in at leaky joints and contaminate the product.

After the successful introduction of a new filtration process, manufacturing tolerances allow reasonable changes in flow rate so long as quality is met. Therefore, the most common production problem is complete plugging of filter media resulting in no productivity. Subtle changes in raw material quality are often at fault. The level of an impurity need change only slightly to create problems with the fine porosity media used in polishing operations. For example, iron contamination in an alkaline product can lead to colloidal precipitates, which blind the media. Raw material problems should always be suspected when synthesis procedures have been altered or when the vendor of a purchased commodity has changed.

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.[12]

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

Surface Tension in Capillary Tubes

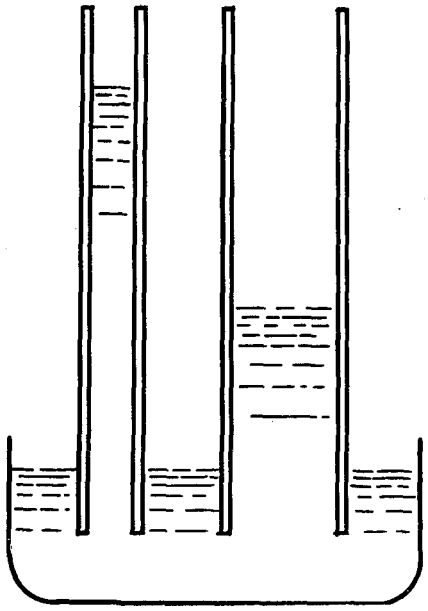


FIG. 7-10. *Surface tension in capillary tubes.*

of a large pore. The same is true for pores in a membrane. The bubble point pressure is governed by the following equation:

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

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)

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.

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.

Diffusion Testing

A diffusion test must be performed in high-volume systems, e.g., cartridges or multistack 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 mem-

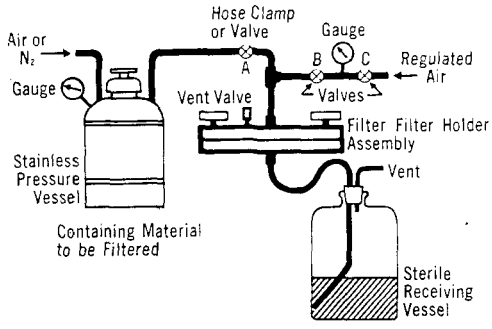


FIG. 7-11. *Connections for nondestructive bubble test to assure that membrane filter is intact. The test does not affect sterility. (Courtesy of Millipore Corporation)*

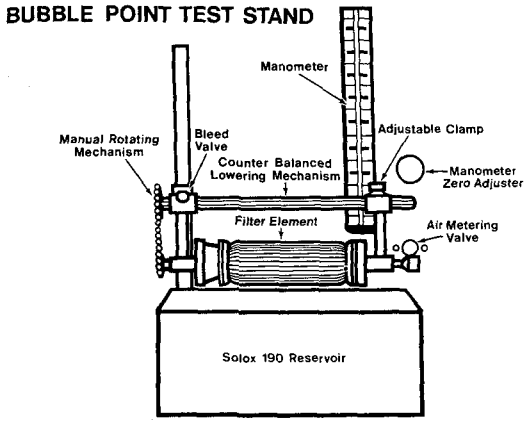


FIG. 7-12. *Apparatus for performing the visible bubble test for cartridge filters.*[26] *(From Field Experience in Testing Membrane Filter Integrity by the Forward Flow Test Methods, Bulletin AB710-1-75. Pall Corporation, NY.)*

brane 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.[23,24]

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.
3. 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.[23]

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).[2,4,26] 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. Porcelain nutzches may be used for collecting sterile crystals or in opera-

tions where slurries are incompatible with metals. Since they are frequently operated under pressure or vacuum, they are not truly gravity filters.

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.

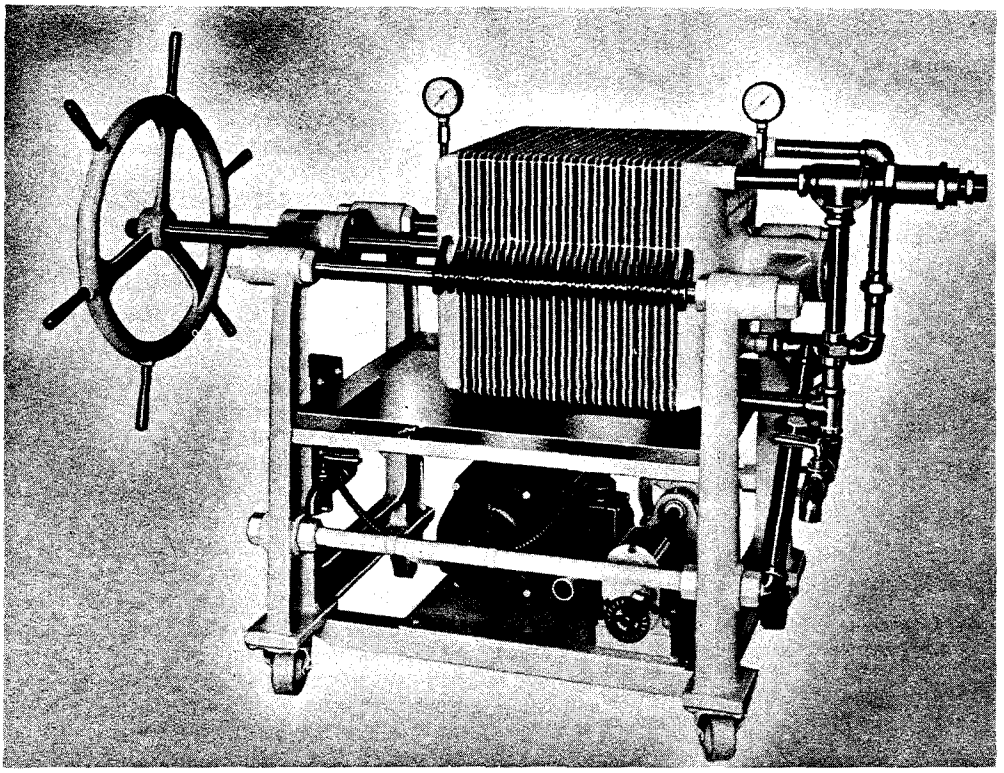
The filter press is the most versatile of filters since the number and type of filter sheets can be varied to suit a particular requirement. It can be used for coarse to fine filtrations, and by special conduit arrangements, for multistage filtration within a single press. The filter press is the most 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 may be 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.[22] 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.

Cartridge Filters and Systems

Cartridge filters have an integral cylindric configuration made with disposable or cleanable filter media and utilize either plastic or metal structural hardware.[26] With the discovery of strong pleatable membranes such as cellulose nitrate, polyamide, polyvinylidene chloride, PTFE, and nylon, cartridge filters have revolutionized the filtration industry. Cartridge filters provide maximum filtration area in the smallest possible package, allow quick changeout of the media, and save time and money. Cartridge filters of different shapes, structures, forms, and sizes for different applications in the pharma-



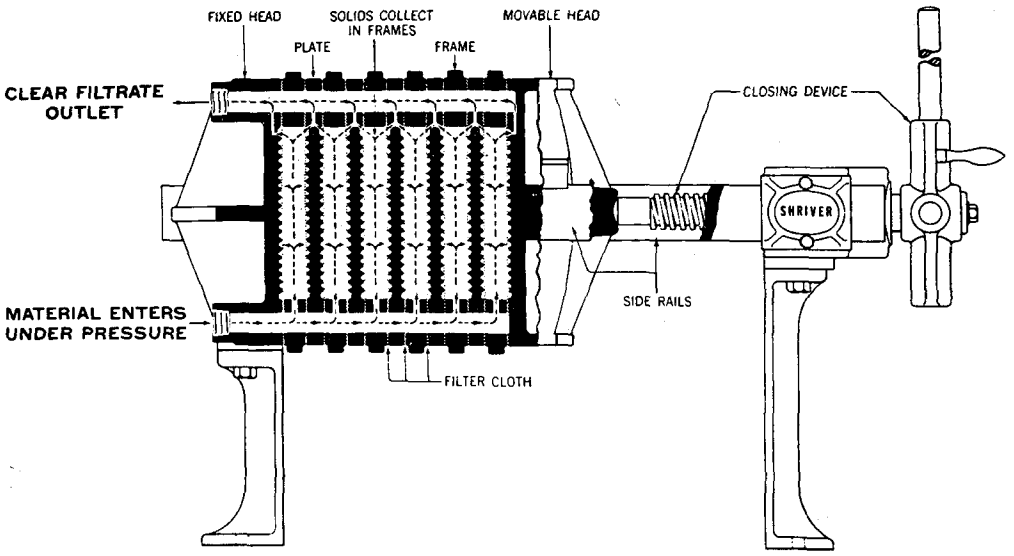


FIG. 7-13. *The plate and frame filter press may have 10 to 100 filtering surfaces and may be filled with pumps, sanitary fittings, sludge frames, or dividing plates for serial filtration. (Courtesy of Ertel Engineering and T. Shriver & Co. Inc.)*

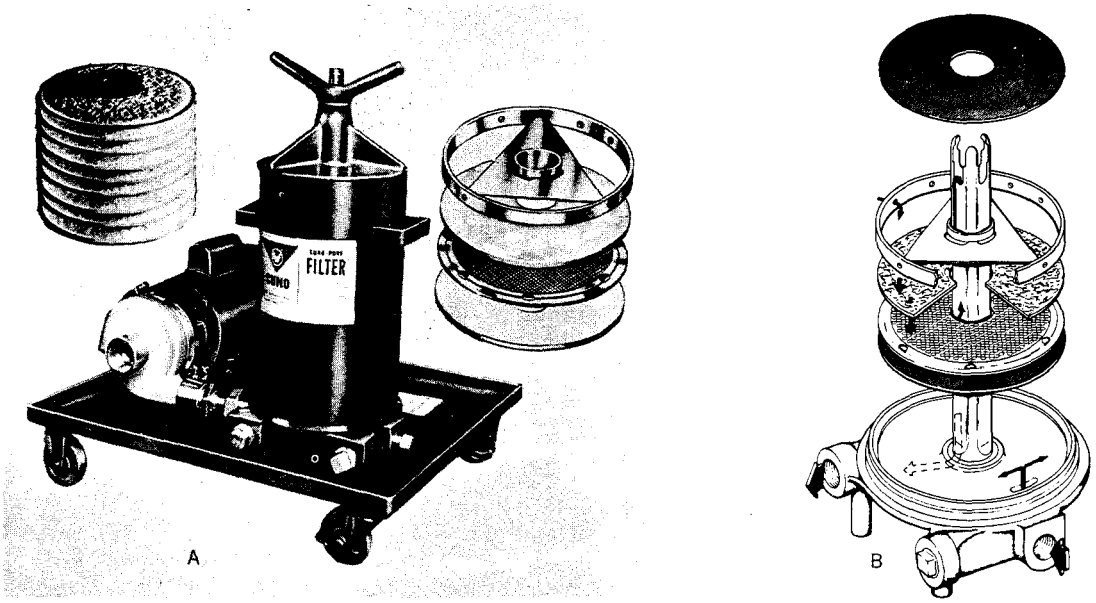


FIG. 7-14. *Disc filter casing* (A) *accommodates precompressed cartridges or disc media. Exploded view* (B) *shows liquid flow through assembled disc. (Courtesy of the Cuno Engineering Corporation.)*

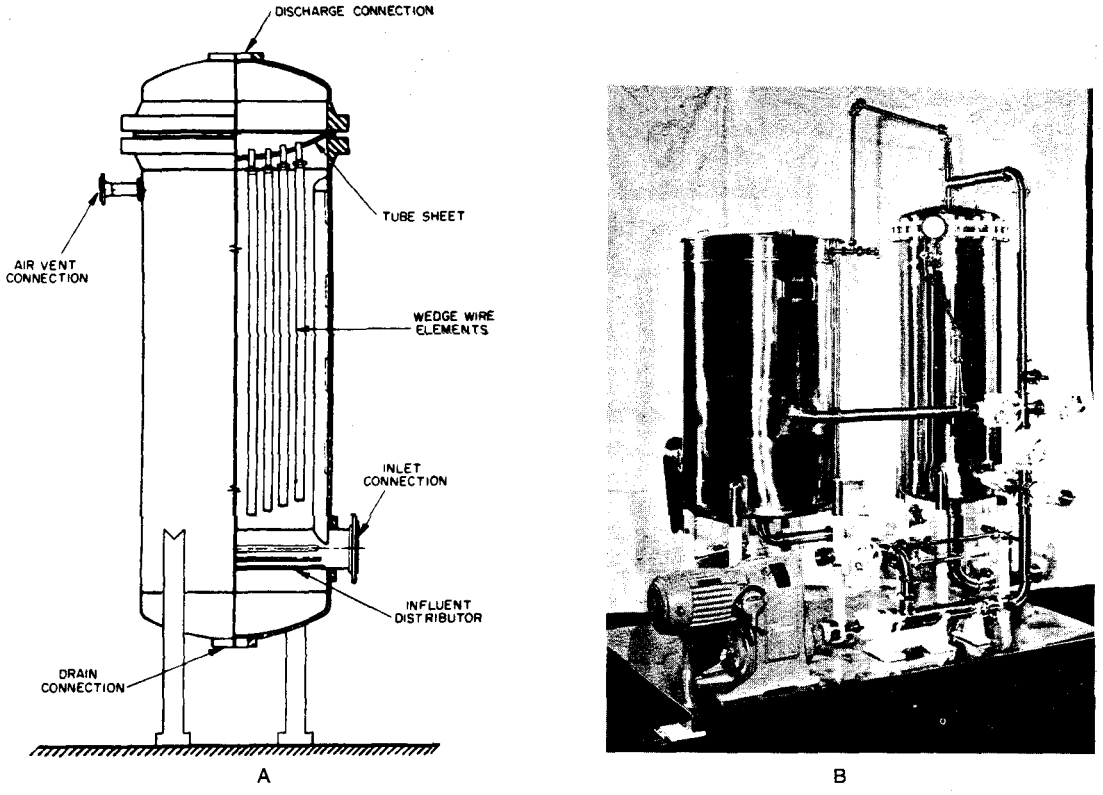


FIG. 7-15. *A precoat pressure filter with wedge wire elements* (A) *is part of all stainless steel filter systems* (B). *Special pump and fittings allow cleaning and sterilization in minutes. (Courtesy of Croll-Reynolds Engineering Co., Inc.)*

ceutical industry are now available in disposable and nondisposable forms.[12,19,27–30] The housings for cartridge filters come in a wide variety of configurations for both micron and submicron filtration. The major differences in various housings are in the design, materials of construction, seals that are used to install the cartridge in the housing, and the application for which they are used in the pharmaceutical industry. The housing for cartridge filters are described in terms of the height of the cartridge and in the number of cartridge receptacles in the base end of the housing. When a user purchases a housing from one manufacturer, he is usually not "locked in" to that manufacturer's cartridges. Adaptors are available that allow the cartridge filter of one manufacturer to fit into virtually any other manufacturer's housing.

Filter media can be formed into cartridge form by either tubular-wound, string-wound, or pleated formation. Alternate layers of filter media and separator material are rolled into a spiral configuration, and by potting the ends of the cartridge, form the "dead-ended" or "cross-flow" type of flow channels. String-wound cartridges are the most commonly used and inexpensive filters available. Pleated cartridges are modified tubular configurations with a large filtration area. A single knife-edge flat gasket may be a satisfactory seal for cartridge filters with 1.0-micron or larger pore size. For submicron filtration, the most satisfactory seal is an O-ring.

Disposable or permanent *cartridge filters* are used for fluid clarification or sterilization. Standard elements for nonsterile filtration may be interchanged between cartridge holders offered by several companies (Fig. 7-16). Increases in capacity result from multi-element holders, and 12 element units are usually adequate for batches of 500 to 1000 gallons. The cost of disposable elements is offset by labor savings inherent in the simplicity of assembly and cleaning of cartridge clarifiers.

The metallic *edge filters*, particularly those with self-cleaning devices (Fig. 7-17), are excellent security filters for suspensions that may plug or blind conventional wire mesh. A cleaning blade combs away accumulated solids, which fall into a sump in the filter casing. A quick-coupling *metal cartridge filter* with construction that prevents short-circuiting of the filter element is also available (Fig. 7-18). The special design permits rapid disassembly as well as interchange of reusable filter media. Metal elements permit particle retention as low as 1.5 microns. Duo filters, two units connected in parallel, are recommended where uninterrupted service is required. A high-frequency vibrator,

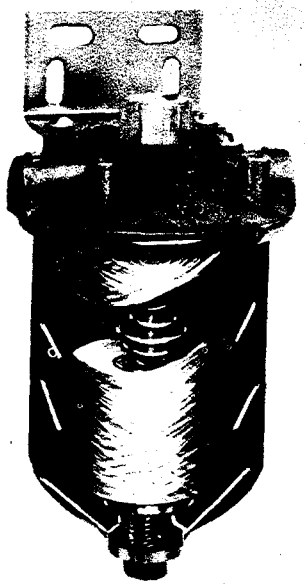


FIG. 7-16. *A disposable wound cartridge is installed in holder. Liquid flows through the element and is discharged through the core. (Courtesy of the Filterite Corporation.)*

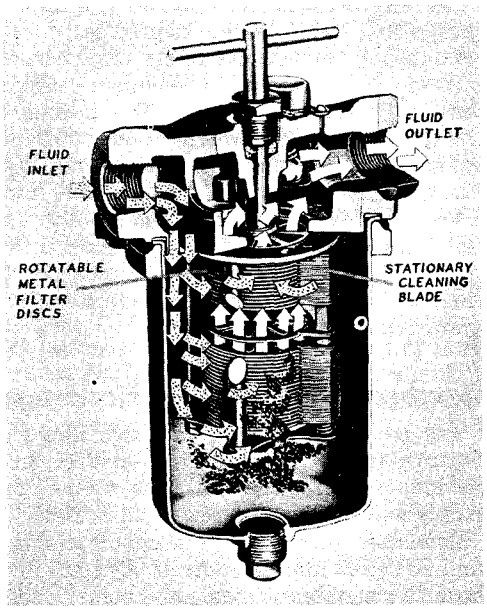


FIG. 7-17. *An edge filter with automatic cleaning device may be automated by replacing handle with motor. (Courtesy of the Cuno Engineering Corporation.)*

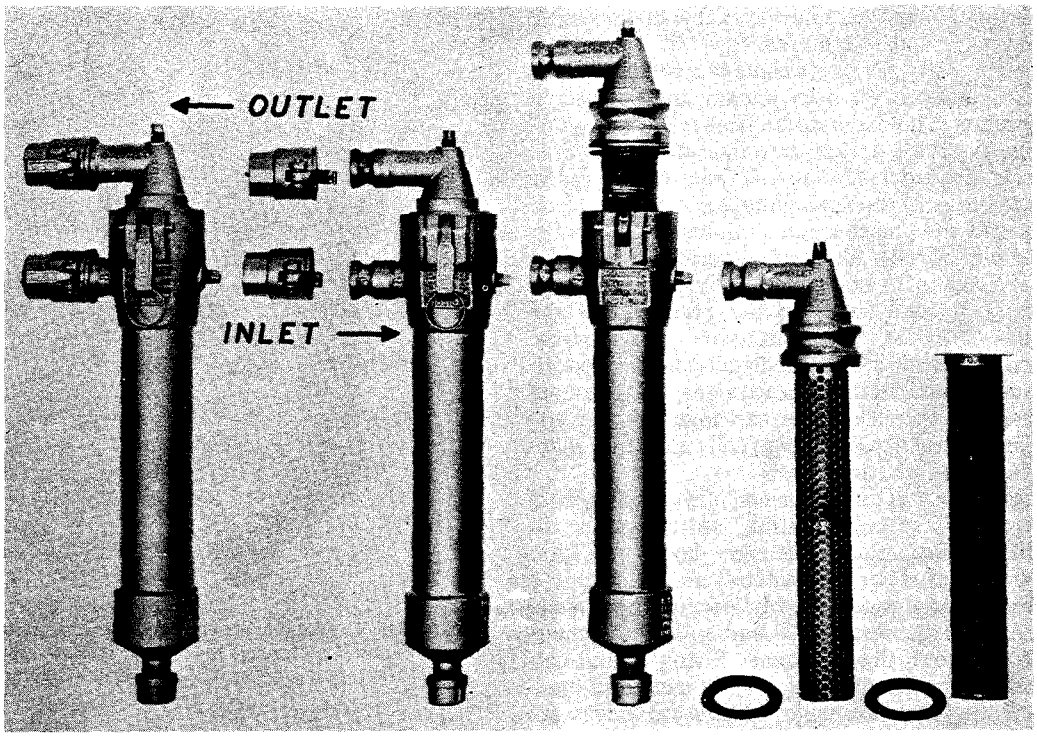


FIG. 7-18. *Quick-coupling cartridge filter for metallic media is readily cleaned. (Courtesy of the Ronnigen-Petter Company.)*

acting only on the element, assists in filtration of slurries that have blinding tendencies.

Vendors of membrane filters offer cartridge units in single- and multiple-element configurations.[21,27–32] These cartridges have become the unit of choice for high-volume, sterile filtrations and are ideal for in-line, final polish prior to bottling of bulk parenterals. Cartridge filters having absolute ratings of 0.04 microns are also available (Fig. 7-19). The latter units have 5 to 10 square feet of effective filtering area per cartridge of 10-inch height, and some can also be steam-sterilized.[27–32]

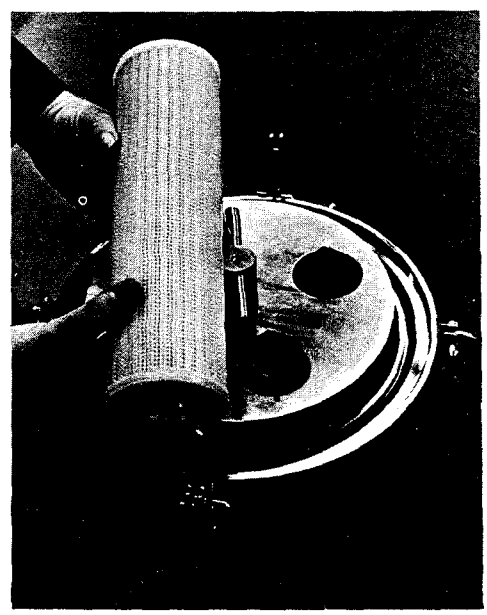


FIG. 7-19. *Multiple-cartridge holders permit high-volume processing. (Courtesy of the Pall Corporation.)*

Membrane Filters and Housings

The use of membrane cartridge filters and housings has been discussed extensively in the previous section. The following section deals mainly with disc membranes and holders.

Membrane filter holders accept membranes from 13 to 293 mm in diameter. A useful rule of thumb for membrane media and holder sizes for various volumes of low-viscosity liquid is shown in Table 7-5. Although 90- or 142-mm units are suitable for moderate volumes, the 293-mm

TABLE 7-5. *Membrane Disc Filter Sizes for Various Volumes*

Volumes	*Filter*
10–100 ml	13- or 25-mm discs
100–300 ml	47-mm discs
300–5,000 ml	90-mm discs
5,000–10,000 ml	142-mm discs
20–1,000 L	293-mm discs
1,000 L and up	cartridges

membrane holder is the usual production choice for small-batch sizes. Stainless steel holders for the sterilizing filter have sanitary connections, and the support screens are faced with Teflon to permit autoclaving with the membrane in place. Special compatibility problems may require polyvinylchloride holders with stainless steel supports, or units that have only Teflon and polypropylene contact parts.[20]

Serial filtration is often desired to fractionate the particulates in a fluid. A membrane of large pore size may often be used as a prefilter for a final downstream membrane filter of a smaller pore size.

Pressure drop across the filter media is often observed. This pressure drop may be contributed by either the filter media, the holder, or the housing. In a properly designed system, the pressure drop due to housing should usually be insignificant except for high-flow liquids or gases.

Laboratory Filtration Equipment

Laboratory equipment catalogs offer a wide choice of funnels and flasks adaptable to pharmaceutical filtration studies. Although a Buchner funnel test permits analysis of the major difficulties in a filtration problem, development laboratories should have additional procedures and apparatus that produce the qualitative conditions expected in large-scale production. This requirement can be met with a nominal capital investment.

For gravity filtration, conventional glass percolators are applicable, in which case the bottom tube is covered with fibrous material. The filtering funnel is the most common of all laboratory filter devices. Filter paper is used with funnels. Sometimes, a plug of fibrous material may be used instead. Filter bags for laboratory use are made of fabric and are mounted for gravity filtration. The uncertainty of adequate clarification with *glass beads* or *sand* has restricted their use as gravity filters for certain operations in the laboratory.

Suction filters are greatly utilized in the laboratory. Usually, a conical funnel and the Buchner funnel are used for suction filtration, as are immersion and suction-leaf filters.[33] Immersion filter tubes, also known as filter sticks, are generally used for small-scale laboratory operations.

Small-laboratory pressure filters have been used substantially in recent years for both sterile and nonsterile filtration operations. Gravity and suction filters are used mostly for nonsterile filtration. For the pressure filtration of small amounts of material, the filter medium may be mounted in a filter tube, with the liquid poured in and pressure applied to the upper surface of the liquid.[34]

Filter paper in circular form is the most common medium for laboratory filtrations. Filter papers are available in a wide variety of textures, purities, and sizes and are available for different uses. They may be circular (1 to 50 cm in diameter), folded, or arranged in sheets or rolls. Among the special types of laboratory filter paper for pharmaceutical industry are:

1. Filter papers impregnated with activated carbon for adsorption of colors and odors in pharmaceutical liquids.
2. Filter paper impregnated with diatomaceous earth for removal of colloidal haze from liquids with low turbidity.

Minimum laboratory equipment includes a plate and frame press, a membrane filter holder, and a single-element housing for disposable cartridges. A 6- or 8-inch, stainless steel filter press with four to eight filter surfaces and sludge frames is adequate. This covers the flow range from 8 to 200 gallons per hour with minimum filtrate holdup in the press. Stainless steel construction permits autoclaving for sterile operations. Auxiliary equipment for mixing filter aid and feeding the press (10- to 20-gallon tanks, agitators, and centrifugal pump) should also be available. A 90-mm, stainless steel membrane filter holder processes 1 to 15 gallons of sterile solutions per hour. The support plate should be Teflon-lined to permit autoclave sterilization with membranes in place; the gaskets should also be Teflon. Integrity testing apparatus and a stainless steel pressure vessel of 1- to 5-gallon capacity are essential auxiliaries. The same pressure assembly may be used in cartridge filter tests. A broad selection of media should be on hand for each unit.

More flexibility is obtained by adding a metal cartridge filter and a small, manually operated, self-cleaning, edge filter. If processing of high-

volume cosmetic products is expected, a single-leaf, precoat pressure filter should be available. Units can be obtained with capacities as low as 1½ gallons.

Cake Filtration

Cake filtration in which solids recovery is the goal is an important pharmaceutical process. Personnel involved in synthesis or fermentation to produce bulk active ingredients consider cake filtration to be the primary aim of the unit operation. Engineering textbooks and current literature stress the theory, laboratory test methods, and equipment required for solids separation.[2,4,26]

The plate and frame press and precoat pressure filters used for clarification also are applied to solids recovery. The basic design is often modified to reduce the high labor factor. In general, these pressure filters are restricted to batch operation and recovery of moderate weights of expensive materials.

For large-scale operations, continuous vacuum filters are most widely used. The *rotary-drum vacuum filter* is divided into sections, each connected to a discharge head. The slurry is fed to a tank in which solids are held in suspension by an agitator. As the drum rotates, each section passes through the slurry, and vacuum draws filtrate through a filter medium at the drum surface. The suspended solids deposit on the filter drum as a cake, and as rotation continues, vacuum holds the cake at the drum surface. The cake is washed and dried as it moves toward the discharge point. It may be scraped from the drum or it may be supported by strings until it breaks free under gravitational forces. Many variants of the basic design are needed to accommodate differences in cake formation, drying rates, and discharge properties.

Filtering centrifuges are another general class of solids recovery devices. In this method of filtration, centrifugal force is used to affect the passage of the liquid through the filter medium.[33] This type of filtration is particularly advantageous when very fine particles are involved. This device is fitted with a perforated basket, which supports the filter media. The basket revolves inside the casing. Slurry is sprayed into the basket, in which centrifugal action forces the filtrate through the media on which the cake deposits. Continuous discharge of solids is possible, but batch units that require shutdown for removal of solids are also common. Whenever solids recovery is the primary goal, centrifuges must be considered as an alternative to filtration.

Membrane Ultrafiltration

Membrane ultrafiltration has become a commercially feasible unit operation in the past decade.[10,12,13,19,22,30,35–38] Unlike conventional filtration, ultrafiltration is a process of selective molecular separation. It is defined as a process of removing dissolved molecules on the basis of membrane size and configuration by passing a solution under pressure through a very fine filter. Ultrafiltration membrane retains most macromolecules while allowing smaller molecules and the solvent to pass through the membrane, even though the membrane is not rated as absolute. The difference between microfiltration and ultrafiltration is significant. The former removes particulates and bacteria; the latter separates molecules. Application of hydraulic pressure reverses the normal process of osmosis, so that the membrane acts as a molecular screen through which only those molecules below a certain size are allowed to pass.

Separation of a solvent and a solute of different molecular size may be achieved by selecting a membrane that allows the solvent, but not the solute, to pass through. Alternatively, two solutes of different molecular size may be separated by choosing a membrane that passes the smaller molecule, but holds back the larger one (Fig. 7-20). Ultrafiltration is similar in process to reverse osmosis; both filter on the basis of molecular size. Ultrafiltration is different from reverse osmosis in the sense that it does not separate on the basis of ionic rejection. Dialysis and ultrafiltration are similar in the sense that both processes separate molecules, but ultrafiltration is different in that it does involve the application of pressure.

The selectivity and retentivity of a membrane are characterized by its molecular weight cutoff. It is difficult to characterize the porosity of an ultrafiltration membrane by means of precise molecular weight cutoff. The configuration of the molecule and its electrical charge may also affect the separation properties of the membrane.[30] Ultrafiltration membranes are therefore rated on the basis of nominal molecular weight cutoff. The shape of the molecule to be retained plays a major role in retentivity. Many of the same techniques that are used in microfiltration to increase flow rate and throughput are also used for ultrafiltration. Ultrafiltration membranes are available as flat sheets, pleated cartridges, or hollow fibers. The hollow fibers have the selective skin on the inside of the fiber.

Industrial use of this procedure has followed the development of anisotropic polymer membranes in a variety of biologically inert, noncel-

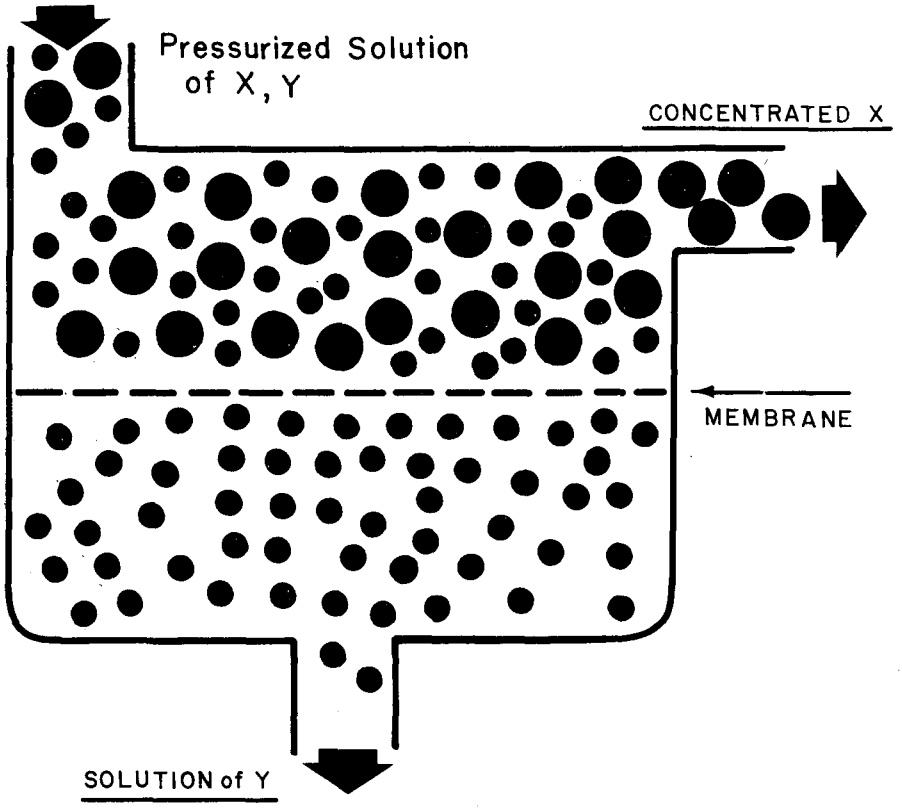


FIG. 7-20. *Schematic diagram of membrane ultrafiltration process.*

lulosic materials. These membranes are fragile structures, however, and usually require a backing plate of porous material to withstand operational pressure. During the processing of a solution, a region of high solute concentration also develops at the surface of the membrane, resisting further passage of solvent. Providing essential support for the membrane and overcoming concentration polarization through shear effects have resulted in a wide variety of commercial apparatus, including tangential-flow cassette systems, process ultrafiltration cartridges, hollow fiber beakers, and collodion bags. Since the technology continues to change rapidly, reliance on technical expertise of the manufacturer is advisable.

Applications in the pharmaceutical industry are predominantly in the concentration of heat-labile products, such as vaccines, virus preparations, and immunoglobulins. Ultrafiltration also has been used to recover antibiotics, hormones, or vitamins from fermentation broths, to separate cells from fermentation broth, to clarify solutions, and to remove low-molecular-weight contaminants prior to using conventional recovery techniques. The most important application of ultrafiltration is the removal of pyrogens.

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SECTION II

Pharmaceutical Dosage Form Design