concentration, however, may be achieved at reason-
able cost by electrodialysis.

**Electrodialysis in the Food and Chemical Industry**

Several applications of electrodialysis in the food indus-
tries, such as the demineralization of cheese whey, have
considerable economic significance and are well estab-
lished today. Other applications, such as the
deshashing of molasses or de-acidification of fruit
juices, are still in an experimental stage. In the chem-
ical industry electrodialysis is used for the desalina-
tion of protein, dextran or sugar solutions. Here,
electrodialysis is often in competition with other sep-
aration procedures such as dialysis and solvent
extraction. The separation of organic acids is an ap-
plication of electrodialysis that is of interest to the
pharmaceutical industry.

**Production of Ultra Pure Water**

Electrodialysis is now being used for the produc-
tion of ultra pure water for the semiconductor industry.
By combining electrodialysis with mixed-bed ion ex-
change resins, deionized water is obtained without
a chemical regeneration of the ion exchange resin.
The process has been commercialized recently.

**Conclusions**

Electrodialysis has a long and proven history in
the desalination of brackish waters. However, new
applications in waste water treatment as well as in the
food and the chemical industry are becoming more
and more important. There are still a multitude of
problems to be solved. Some are related to the proper-
ties of the membranes and the process design, while
others are caused by the lack of application know-
how and practical experience.

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**Filtration**

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Morganville, NJ, USA

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**Introduction**

Filtration is a key processing operation in the pharma-
ceutical, chemical and cosmetic industries. For
example, filtration may be necessary to clear process
solutions before analysis or as process step in manufac-
turing or in the sterilization of process solutions. Ana-
lytical testing requires only laboratory-scale filtration
and is usually performed by a variety of membrane
types depending upon the application. Filtration in
manufacturing requires large-scale filtering in engin-
eered devices called membrane modules or cartridges.

**Filtration Mechanism**

Filtration is a mechanical phenomenon, which is
sometimes aided by chemical manipulations of the
filtration medium to make it more efficient. In
any case, a driving force across the filter media is
required. The following methods can be used to gen-
erate this driving force:

- Vacuum
- Pressure difference
- Centrifugal force
- Gravity pull
- Concentration difference
- Electrical potential difference
- Temperature difference
- A specific chemical attraction–repulsion
Filtration is either through a membrane or bed of filter media. The chemical composition of the filter media and physical conditions to perform the filtration constitute a large number of filtration choices available today.

**Membrane Filtration**

Membrane filtration through a very thin filter medium is also known as ‘surface filtration’. The solid particles to be separated are usually large compared to the pore size characteristic of the membrane. The pores on the surface are of irregular shapes. The rejection of particles is dependent on several factors affecting the transport through these pores into the tortuous channels. The separation is based on exclusion discrimination by physical size, charge or affinity or a combination of these properties. Large particles are rejected on the surface and do not accumulate on the surface and do not get a chance to enter into the interior of the filter.

Other types of membrane filters are screen filters and here the pores do not lead into tortuous capillary paths. The pore size is uniform but the distribution of the pores is random on the filter surface. The filter is made by bombarding a thin polycarbonate film with neutrons in a reactor. The film is then placed in a bath of etching solution which preferentially attacks the polymer along the track of the neutrons. The pore size is regulated by selecting the appropriate reagent, exposure time and temperature.

Membrane filtration can be dead end or cross-flow. In dead-end filtration all the solution is forced through the membrane. Retained particles collect on the membrane surface and in the filter greatly reducing flow. A current application of dead-end filtration is in bacterial testing where the liquid to be tested is passed through the filter retaining all bacteria on the surface. Most chromatographic filtration applications are of this type. In cross-flow membrane filtration, the feed liquid flows tangentially to the membrane surface, which prevents the build up of cake on the membrane. Both types of filtration use similar membranes.

By convention, membrane filtration or microfiltration is limited to membranes used to remove particles larger than 0.1 μm in diameter. Membranes able to remove smaller particles are called ‘ultrafiltration membranes’ and microsolute can be removed by reverse osmosis. Ultrafiltration and reverse osmosis are discussed elsewhere. This article is limited to the process of microfiltration.

The filtration thresholds of common membrane-filtration processes are shown in Table 1.

### Table 1 Filtration threshold of common membrane-filtration processes

<table>
<thead>
<tr>
<th>Type of filtration</th>
<th>Impermeability of membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverse osmosis</td>
<td>&lt; 0.001 μm</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>0.001-0.1 μm</td>
</tr>
<tr>
<td>Microfiltration</td>
<td>0.1-10 μm</td>
</tr>
</tbody>
</table>

**Microfiltration**

Microfiltration is used to separate suspended solids or colloidal particles between 0.1 and 10 μm in diameter from solution. Most of the chromatography applications are microfiltration based. The same type of membrane with different pore size is used for these applications. The membrane acts like a physical sieve. The fluid passes through tortuous channels while the particles are rejected on the surface of the filter. It can be easily understood as a mechanical sieve with pores leading into a capillary forming a tortuous path; within this tortuous path, there could be mechanical entrapment and adsorption (Figure 1).

Microfiltration membranes can be subjected to harsher conditions compared to ultrafiltration membranes. Membranes of different polymers in varying pore sizes are available. Even nominally the same pore-size membranes of a polymer may differ from each other in filtration characteristics because they may have different pore-size distributions, i.e. varying pore size all across the membrane. To aid in wetting, many membranes have some surfactant pretreatment and their effective pore size may be different from the real pore size. Often a membrane filter becomes more efficient as small particles are entrapped within the pores. The large particles captured on the filter can also alter the effective particle-size rejection in subsequent filtration. Filter capacity may vary depending on the solute particle-size variation in the feed. Uniform size particles result in faster clogging of filters.

**Depth Filter**

In depth filtration, the filter medium has larger pores than the particles it is meant to remove. The process starts out at the surface of the filter and proceeds in the cake portion of the membrane. The medium traps the particles in the interstices of the internal structure. Particles enter into the filter medium and separate by gravity settling, diffusion, and attachment to the media owing to electrostatic forces. These filters usually have a pressure drop across the filter caused by pressure, vacuum, or centrifugation. These filters usually have a long life, but
eventually a cake is formed over the medium stopping the flow through the filtration device. When the filter bed is full of solids and the pressure drop is very high, the entrapped solids can be back-washed. Usually less than 0.1% solids concentration is filtered through this type of filter to avoid pressure build up. There is always some liquid left behind in depth filters and some solid material still makes it through the filter medium depending upon the efficiency of the system. To use the system effectively, variations of this procedure using moving-bed filters, radial flow filters, or travelling back-wash filters can be employed. The commercial products available for this kind of filtration are application specific.

**Filtration Matrices**

A variety of polymers are used to manufacture filter media. Each type has specific attributes and could be best for certain applications but could be a complete failure for other applications. The same filter material from different manufacturers can differ in physical properties and in filtration characteristics. However, the chemical compatibility of the material is almost the same irrespective of the manufacturer (Table 2).

Incompatible chemicals can cause shedding, affecting pore size, as well as adding extractables. Hydrophobic membranes have to be wet before starting the filtration. In some cases, it is desirable to convert the hydrophobic membranes into hydrophilic membranes by modifying the surface. Surface reactions can also be used for changing the surface charge. The polyvinylidene fluoride (PVDF) membranes can be treated to render them hydrophilic and can be reacted to modify the surface charge. The use of aggressive solvents should be avoided with these filters to minimize deterioration of the surface. Membranes used in filtration usually have surface-active agents incorporated in them to make the pre-wetting easier.

**Filtration Devices**

The filtration application dictates the type of device to be used. Industrial applications demand a high surface area, ease of cleaning and low clogging. For enhanced yield and capacity, open-channel tangential flow systems, which require two pumps for recirculation and permeation, are available from several manufacturers. Different designs are used to overcome gel formation and to continuously sweep away the contamination in the filtration process. The details of these systems are beyond the scope of this article.

The most common disposable filtration devices used in laboratories are syringe filters. The membrane is held in a polypropylene housing with an adapter for syringe attachment on one end. This adapter can be a luer lock or friction fitting. The other end is designed for easy extrusion of permeates. The filter membrane can be housed alone or with pre-filters. The membrane is bonded to the housing ultrasonically, without the use of any chemical adhesive, to avoid unwanted extractables in the filtering process. Syringe filters are disposable and used in very high volume, particularly in the pharmaceutical industry. Because the continuous use of syringe filters
Table 2 Chemical compatibility of common filter membranes with widely used solvents

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Nylon</th>
<th>PTFE</th>
<th>PVDF</th>
<th>PS</th>
<th>Polypropylene</th>
<th>Regen. cellulose</th>
<th>Cellulose nitrate</th>
<th>Cellulose acetate</th>
<th>Cellulose triacetate</th>
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<tr>
<td>Acids</td>
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<td></td>
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<tr>
<td>Glacial acetic acid</td>
<td>LC</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>NC</td>
<td>NC</td>
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<td>Hydrochloric acid</td>
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<td>C</td>
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<td>C</td>
<td>C</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
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<tr>
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<td>C</td>
<td>NC</td>
<td>NC</td>
<td>C</td>
<td>NC</td>
<td>NC</td>
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<td>NC</td>
<td>C</td>
<td>NC</td>
<td>NC</td>
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<td>Phosphoric acid (25%)</td>
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<td>C</td>
<td>C</td>
<td>NC</td>
<td>C</td>
<td>LC</td>
<td>LC</td>
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<td>C</td>
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<td>Ammonium hydroxide (25%)</td>
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<td>C</td>
<td>LC</td>
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<td>LC</td>
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<td>Sodium hydroxide 3 mol L⁻¹</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>LC</td>
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<td>Sodium hydroxide 3 mol L⁻¹</td>
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<td>NC</td>
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<td>Benzyl alcohol</td>
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<td>C</td>
<td>C</td>
<td>ND</td>
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<td>C</td>
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<td>C</td>
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<td>Carbon tetrachloride</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>NC</td>
<td>LC</td>
<td>C</td>
<td>C</td>
<td>LC</td>
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<tr>
<td>Chloroform</td>
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<td>LC</td>
<td>C</td>
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<td>C</td>
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<td>C</td>
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<td>Dimethylformamide</td>
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<td>NC</td>
<td>C</td>
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<td>NC</td>
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<td>DMSO</td>
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<td>NC</td>
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<td>C</td>
<td>C</td>
<td>NC</td>
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<tr>
<td>Ethanol/methanol</td>
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<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>LC</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Ethyl acetate</td>
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<td>C</td>
<td>NC</td>
<td>LC</td>
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<tr>
<td>Ethyl ether</td>
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<td>LC</td>
<td>NC</td>
<td>C</td>
<td>C</td>
<td>NC</td>
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<td>Glycerol</td>
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<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Hexane</td>
<td>C</td>
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<td>C</td>
<td>NC</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Isopropanol</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>LC</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Methyl ethyl ketone</td>
<td>C</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
<td>ND</td>
<td>C</td>
<td>LC</td>
<td>LC</td>
<td>LC</td>
</tr>
<tr>
<td>Tetrachlorofuran</td>
<td>C</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
<td>C</td>
<td>C</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

*PTFE, polytetrafluoroethylene; PVDF, polyvinylidene fluoride; PS, polysulfone. C, compatible; LC, limited compatibility; NC, non-compatible; ND, not done; MF, microfiltration; UF, ultrafiltration; RO, reversed osmosis.

can be tiring, a mechanical device is now available which is helpful when repeated filtration is required.

Another common type of laboratory filtration is with centrifuge filters. These devices are the method of choice for molecular weight cut-off filtration and for the filtration of viscous materials. The driving force here is centrifugal force. The filter is manufactured to fit in the rotors of laboratory centrifuges. In these rotors, several filtrations can be carried out simultaneously.

**Filtration Applications**

In every type of filtration process, the result is always a retentate (restricted to pass through the filter media) and permeate (downstream collection). Retentate or permeate can be the desired product of the process.

**Selective Filtration**

Selective filtration is used to retain only a particular type of solute. Usually in these cases membranes are modified for the desired affinity. There are several applications and products available based on ionic attraction.

**Purifying Water**

The constantly increasing demand for drinking water requires the sea or other sources to be converted into potable water. Most of the potable water plants use reverse-osmosis treatment. Water used in injectables, buffers and chromatography generally has very defined specifications. For most laboratory applications, water with an electrical resistance of not less than 18 MΩ is required to be pyrogen- and bacteria-free. The water used in chromatography should be free of UV/vis-absorbing and ionic impurities.

**Chromatographic Applications**

Filtration is required in chromatography for preparing a sample for injection. The preparation may include concentration and/or purification. Sample filtration helps in trouble-free operation of chromatography instruments and columns. The use of filtration
for processing samples and solvent is an essential part of instrument preventive maintenance programmes. The filtration of the mobile phase also results in degassing, which is essential for long pump life in high pressure liquid chromatography. The most common devices used for sample preparations are syringe filters.

**Biological Applications**

The use of filtration as a sterilizing technique is becoming increasingly popular. Other sterilization techniques such as autoclaving, radioactive exposure or ethylene oxide treatment can be detrimental for the product. A dead-end filtration of instrument preventive maintenance programmes. Other sterilization techniques such as autoclaving, radioactive exposure or ethylene oxide treatment can be detrimental for the product. A dead-end filtration can be detrimental for the product. A dead-end filtration of instrument preventive maintenance programmes. Other sterilization techniques such as autoclaving, radioactive exposure or ethylene oxide treatment can be detrimental for the product.

Viruses can permeate through the membrane of 0.22 μm pore-sized membrane is considered good for sterilizing by filtration. Viruses can permeate through the membrane of 0.22 μm pore-sized membrane is considered good for sterilizing by filtration. Viruses can permeate through the membrane of 0.22 μm pore-sized membrane is considered good for sterilizing by filtration. Viruses can permeate through the membrane of 0.22 μm pore-sized membrane is considered good for sterilizing by filtration.

Filtration is also used for desalting or buffer exchange of proteins and nucleic acids, deproteinizing samples, screening natural products and combinatorial products, and separation of oligonucleotide primers from nucleic acid preparations.

**Selecting the Right Filtration System**

Each application requires a specific filtration characteristic. Choosing the right filtration device and media are necessary when selecting the correct filtration system. The following considerations help when deciding which filter device is to be used:

- **Objective of filtration.**
- **Sample size.**
- **Filter parameters required: permeability, capacity and flow rate.**
- **Physical conditions to which the filtration is required to be subjected.**
- **Tangential flow filter or dead-end filter.**

The choice of filter material, pore size and physical conditions depends on the following factors:

- **The chemical and physical condition of the feed.**
- **Size and shape of molecules.**
- **Zeta potential and isoelectric point.** Filtration carried out at a pH close to the isoelectric point results in reduced electrostatic interactions.
- **Hydrophobicity or hydrophillicity.**
- **Solvent in which solute is dissolved.**
- **Properties of the filter feed, pH, viscosity, surface tension, ionic strength, osmolarity and chemical functionality.**
- **Intended use after filtration of the sample.**

Choice is always application specific. For example, in the bacterial examination of water, the purpose is to retain all the particles on the filter surface. A dead-end filtration is used on a 0.2 μm filter. The cross-flow filter is useful for concentrating particles with the removal of solvent. In selecting the filtration system, it is necessary to always consider yield, simplicity, technical reasons and cost.

In some applications, using a combination of different filtration techniques in a certain order is the most efficient method. Sometimes it helps to pre-treat the solution to be filtered. The pretreatment could include coagulation and flocculation, magnetic treatment, pH adjustments, and an electric field. A proper washing procedure is usually employed to have the most efficient filtration.

Two filters supplied by Pall Corporation are shown in Figures 2 and 3.

**Filtration Validation**

The validation of filtration processes includes all the equipment, physical conditions and material requirements of the process. Usually the filter manufacturer performs the basic testing to ensure the type, pore size and integrity of the filter. The filter material characteristics are covered in this article. Some of the most common tests used for this purpose are shown below.

**Bubble Point**

Bubble point is a function of pore size, filter medium wettability, surface tension and angle of contact. The filter membrane is wetted and a gradual increasing gas pressure is applied. The bubble starts forming from the largest pore first. The gas pressure at this time is the bubble point for the membrane. This is an indirect measurement of the size of the largest pore on the filter. It does not indicate the variability of pore sizes or irregularity of the membrane.

**Water Breakthrough**

The water-breakthrough test is used for hydrophobic membranes. It is similar to bubble point as this test also give information about the largest pore of the filter membrane. In this test, the minimum pressure required to permeate water from a filter membrane is measured. The water-breakthrough number is dependent on pre-wetting, temperature and pore size of the filter medium. Water is first permeated from the largest pore. This also ascertains filter usability as an aqueous barrier.
Figure 2  (See Colour Plate 49). Pall Ultipor® VF™ Grade DV50 virus filters for high protein-transmissive virus filtration. (Photo courtesy of Pall Corporation, East Hills, NY.)

Extractables

The filter devices and materials can be a source of contamination in the filtration process. The source of impurities could be additives, stabilizers, surface modifiers, detergents and monomers in the filter material. Some contaminants occur in small quantities but some detergents can make up as much as 2–3% of the dry weight of the filter. This large amount of detergent helps in efficient filtration, lower pressure requirements and permits autoclaving for sterilization. The additives and monomers can be entrapped within the body of the filter. Sometimes the source of impurities is not from the filtering material but from the housing or support of the filter. This housing material is usually plastic, and the manufacturer tests that the plastic used in containing the filter material is not going to leach out impurities under experimental conditions. Although aggressive solvents or physical conditions may be very compatible with the filter membrane, they may affect the filter-containment system.

In some analyses, even a small amount of contaminant is enough to cause problems. Commercial filter manufacturers now certify for specific applications. For many biological applications, the manufacturer certifies the filtration material to be pyrogen-free. For chromatographic applications the filter material is certified not to add impurities to the process. The safest way to use filters for chromatography is to wash them with the same solvent used during filtration and to discard an initial volume of the filtrate. The filters used in ion analysis should be completely free of any ionic impurities. The standard operating procedure of the filtration step should clearly define the conditions and if possible include the limits of the procedure.
Flow Rate

The flow rate is determined by using water or alcohol to determine the permeability to flow before any extra pressure drop produced by the filter cake. Flow rate is dependent on the hydrophobicity of the filter material, temperature of the procedure, physical thickness and pore-size distribution of the filter material. It is expressed as millilitres per minute per square centimeter. An optimum flow rate is needed for the expected life of a filter.

Capacity

Capacity of filtration is the ability to maintain an acceptable permeability. The capacity of a filter is measured until an increase of about three times in differential pressure or ~60% decrease of initial flow. It is expressed as time, volume of liquid, or by quantity of retained particles.

Pore Size

Pore size is probably the most misunderstood property of the filter membrane. The estimation of pore size depends upon the method employed to determine the porosity. The usual methods are all indirect. For a nominal rating, a range of neutral polymers of different sizes is challenged individually on the membrane and the percentage of a particular size retained on the surface rates it for that size. It could be anywhere from 60 to 98% for a given size rating by the manufacturer. The variability of pore sizes is also polymer dependent. The pore sizes are irregular in membranes manufactured by solvent casting. The pore size is averaged to give a mean pore size assuming all pores are circular. The importance of this point is that the efficiency of the filter should be measured above this point. In actual practice, pore size is used only as a guide; retained particle size data are closer to reality in the filtration process. Most filter manufacturers give particle size retained data traceable to standards from the National Institute of Standards and Testing. In membranes manufactured by neutron bombardment, the pores are circular and same-size pores are randomly distributed along the surface of the membrane. The pore size given is the actual pore size of the membrane. In many filter membranes, detergents are used for enhancing filter characteristics; the effective pore size in these membranes is usually larger than the actual pore size.

Microbial Challenge Test

The absolute rating of a membrane is determined by challenging with test organisms (Table 3). The volume of the feed is such that it averages out to one organism per pore on the membrane surface. The absolute rated membrane is accepted if no more than one organism is present in the permeate.

A membrane with a pre-rating of 0.22 μm is acceptable for liquid filtration sterilization. The ability of a membrane to remove bacteria is dependent on the size of the pores and the thickness of the membrane. There is a finite number of specific bacteria, which can be retained by the membrane before it becomes effectively clogged.

Filtration Challenges

Despite the fact that a great deal of improvement in the filtration process and material has taken place,
there are still some areas where any advancement will make filtration a friendlier process.

**Scaling Up for Manufacturing**

The filtration process development remains a challenge because the efficient separation at small volume level is not always transferable to pilot or production scale with the same efficiency and chemistry. Several manufacturers claim new scalable technologies providing similar results in large scale as applications using tangential flow with the same fibre material used throughout the development of the filtration process. Special filtration scale-up software is available commercially.

**Membrane Fouling, Gel and Cake Formation**

The filtration membranes may start fouling during use. This means that particles start attaching on the surface and in the internal porous structure of the membrane. Large suspended or colloidal particles usually are the cause of fouling. Fouling is a result of van der Waals forces, electrostatic attraction, or hydrogen bonding. The fouling of filter media results in a reduction in membrane permeability and uncontrolled solute removal efficiency. The pretreatment of the feed can be helpful in delaying or completely avoiding fouling. Gel formation and cake formation on the surface can be reversible and filter media can be reused. Macromolecules and some interacting small organic molecules can result in gel formation on the filtration surface.

**Cleaning the Filter Media**

It is not cost effective to clean the filter in laboratory-scale filtration. For large-scale filtration, usually cleaning and validation protocols are used. The cleaning process could involve cleaning with detergents or other strong chemicals. It could also involve treating with proteolytic enzymes to break down protein impurities trapped in the filter medium and EDTA to arrest activity of bacterial enzymes. Development of cleaning procedures and validation of filter media is very application specific and requires experienced people to design and implement.

**Extractables**

The extractables in the filter medium can create a problem in the subsequent use of the permeate. This remains a problem in some filter media where additives are used for improved performance. The origin of extractables is either in the processing or the housing device of the filter. Various kinds of extractables are found, including metals, oligomers, loose polymers, plasticizers, wetting agents, antioxidants, resins, fillers and mould-release chemicals. The usual practice is to wash off the filter material immediately before use. The type and amount of impurity in filter media is not consistent. Each type of impurity has its own rate of extraction from the medium. Hence there is no universal filter-treatment procedure which can ensure a contamination-free permeate. The washing procedure could be under- or overdone in certain applications. The challenge exists to manufacture consistent contamination-free filter media.

**Conclusion**

Tremendous developments have taken place in both laboratory and large scale filtration techniques in recent years. Various new types of matrices have been exploited for filtration applications. The heavy use of filtration in industry has clearly identified the challenges that remain to be solved. Research continues on selective filtration as a cost-effective way of separation for various applications. In the next few years, we will witness improvement in both the chemical and mechanical properties of filtration equipment.

*See Colour Plates 49, 50.*

*See also: II/Membrane Separations: Microfiltration; Ultrafiltration.*

**Further Reading**


