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1. INTRODUCTION/SCOPE STATEMENT

Sterilizing filtration of a process gas stream is defined as the complete removal of all microbiological contaminants, excluding viruses. Under certain circumstances, other contaminants such as viruses and plasmids can also be removed by filtration. Thus, in the pharmaceutical industry, particularly in the production of parenterals, there is a wide range of processes for which sterilizing filtration of air or other process gases is appropriate and applicable.

Early and careful screening of potential filter types and configurations can result in fewer technical and regulatory problems, fewer delays, more efficient processing and greater sterility assurance. Although other types of filters can be employed in the control of particulate matter and removal of liquid droplets by coalescence, the focus of this technical report is limited to hydrophobic membrane filter elements. The objective is to assist the reader in the selection, qualification, and validation of a filter that is appropriate for the application on hand. While most gas applications use hydrophobic filters, this does not preclude the use of hydrophilic filters in dry gas systems. For further information on the use of hydrophilic filters, refer to PDA Technical Report No. 26.

This report is intended to complement PDA Technical Report No. 26: *Sterilizing Filtration of Liquids*, and like other PDA Technical Reports it should be considered an educational guide rather than a mandatory or implied standard.

2. HISTORICAL BACKGROUND

Filtration of air and other gases has always been used in a wide range of applications within the pharmaceutical and biotechnology industry. The first generation of gas filtration used depth filters, such as cotton wads or glass fiber, ranging in scale from small plugs within tubes or bottles to large packed towers. Typically, such depth filters were used in conjunction with elevated temperatures to prevent condensation of moisture within the filter medium.

The second generation of gas filters consists of depth cartridges of borosilicate or polypropylene composition. These cartridges are available in configurations that are easier to use, and they provide improved operator handling and safety. They also have more consistent retention characteristics as a consequence of improved non-woven media (fleece) technologies and more appropriate methods of construction. The retention capability of

such cartridges can typically be verified by oil droplet aerosol challenges such as the DOP (dioctyl phthalate) test (discussed later in Sections 8.3). Nevertheless, the depth media of these second-generation cartridges continues to present some limitations, particularly with regard to the potential for bacterial breakthrough. This led to the development of hydrophobic membrane filter elements.

Compared to the earlier depth media, hydrophobic membrane materials have the advantage that they are inherently more resistant to water blockage. While some of the early membranes had to be rendered hydrophobic by silicone coating or similar surface treatment, membranes made of inherently hydrophobic polymers have been available for over two decades. The most common polymers used for the production of hydrophobic membranes are polytetrafluoroethylene (PTFE), polyvinylidene fluoride (PVDF), polypropylene (PP), and polyethylene (PE). Hydrophobic membranes can be produced in more defined ranges of retention ratings than depth media, and their retention capability is considerably less dependent on operational parameters such as moisture content or differential pressure imposed during their use. Filter elements are available in various user-friendly configurations, including tubular, stacked disk, and pleated cartridges. One additional advantage over depth media is that the retention capability of hydrophobic membrane filters can be correlated to physical non-destructive integrity tests, as discussed later in this report.

3. HOW GAS FILTERS WORK

3.1 Size Exclusion

In gas filtration, as in liquid filtration, size exclusion (also referred to as sieve or mechanical retention) is one of the mechanisms of particle retention from a dry gas stream. As the name implies, this mechanism applies to particles that are too large to penetrate a given pore they encounter along the tortuous path through the filter material. Providing the particle is not deformed in the filtration process, this type of retention is independent of the velocity of the air stream through the filter. Retention by size exclusion is illustrated in Figure 1.

3.2 Retention of Smaller Particles

Retention of particles smaller than the actual pore size from a gas can occur by several additional mechanisms, such as diffusional interception, inertial impaction, and electrostatic attraction. These mechanisms capture particles that come in contact with—or close enough to—the filter material for relatively strong binding forces to come

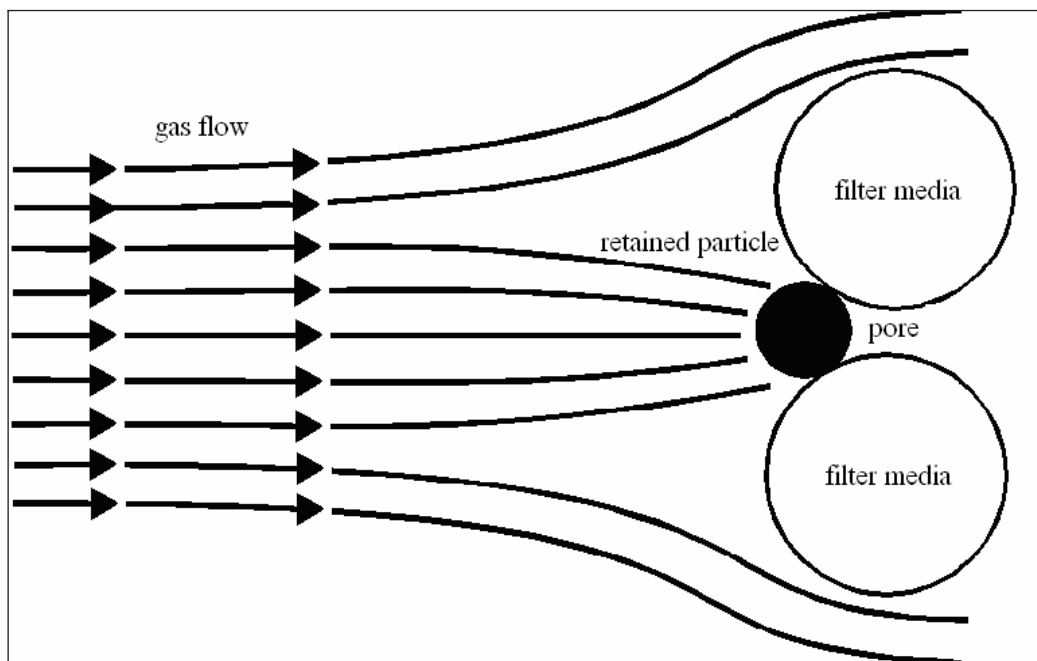


Figure 1: Particle Retention by Size Exclusion

into effect. These additional mechanisms are always present, but their contribution to the overall retention efficiency depends strongly on the size of the particle in question.

3.2.1 Diffusional Interception

In the diffusional interception mechanism, illustrated in Figure 2, particles stray out of the airflow streamlines due to Brownian motion caused by constant and random bombardment of the particles by air molecules. Brownian motion increases the probability of contact between the particle and the filter medium; hence, it increases the

probability of particle retention. However, Brownian motion becomes more pronounced for smaller particle sizes. Thus, the retention efficiency by the diffusional interception mechanism increases as the particle size decreases.

3.2.2 Inertial Impaction

Figure 3 illustrates the mechanism of inertial impaction. The inertia of the particle keeps it from following the streamlines as the gas circumvents the filter material, causing it to collide with the filter medium. This effect becomes more pronounced at larger particle masses;

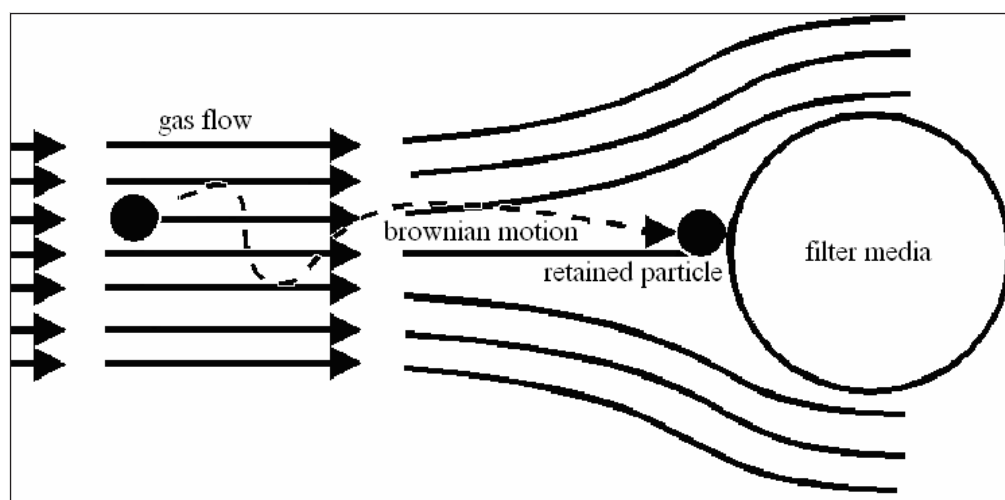


Figure 2: Diffusional Interception

hence, the retention efficiency by this mechanism increases with particle size. In the case of sub-micrometer hydrophobic membranes, the retention of large particles by this mechanism is less significant because these particles are typically retained by size exclusion. In coarse depth filters, however, inertial impaction plays a greater role by retaining particles that are less likely to be retained based solely on size exclusion.

3.2.3 Gravitational Sedimentation

Particles can also deviate from the flow path and collide with the filter media by gravitational sedimentation. Much like inertial impaction, this mechanism is more pro-

Dry air also reduces the danger of condensate build-up within the filter matrix. Airflow velocity is highly important to creating a contact time that is sufficiently long to generate enough separation efficiency for incipient particles to be retained (Grant, 1988).

3.3 Net Retention Efficiency in Filtration of Dry Gases

The net effect on the retention of particles is the sum of the effects observed for the individual mechanisms. At a given gas velocity, very small particles are retained predominantly by diffusional interception. At the particle sizes where this mechanism becomes less effective, iner-

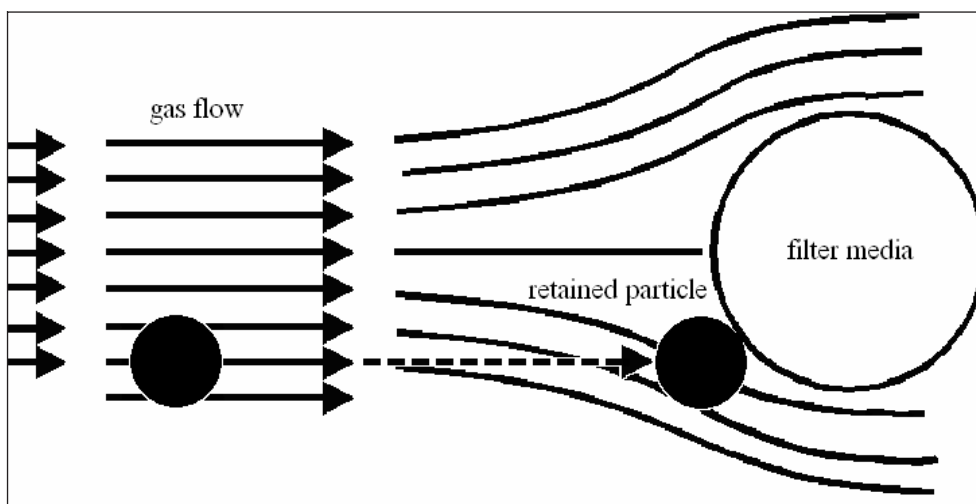


Figure 3: Inertial Impaction

nounced for larger particles, particularly those of high density. In the case of sub-micrometer hydrophobic membranes, this mechanism is not very important, since particles of the size normally retained by gravitational sedimentation (as is the case in depth filters) are more likely retained by size exclusion.

3.2.4 Electrostatic Attraction

Depending on the nature of the particle and the filter material, intermolecular forces may retain particles that come in close proximity to or in contact with the filter material. They will be firmly retained, even during pressure pulsations, because the binding forces are many times stronger than the drag exerted by the gas stream flow upon the particle. Particularly, in the case of HEPA (High Efficiency Particulate Air) and ULPA (Ultra Low Penetration Air) filters, which are not within the scope of this document, electrostatic capture of particles of opposite charge is an effective mechanism. The effectiveness of such filters depends on two major parameters, the humidity of the air and the velocity. Humidity must be low because electrostatic charges are highest when air is dry.

tial impaction, gravitational sedimentation, and size exclusion become more pronounced. The size range in which the transition from diffusional interception to inertial impaction typically occurs includes particles of a size that are not captured by either of these retention mechanisms, as illustrated in Figure 4. The size of the particle least likely to be retained is termed the Most Penetrating Particle Size (MPPS).

The MPPS will not only depend on the type of filter material, but also on the gas velocity through the filter. Brownian motion becomes less pronounced at higher velocities and pressures; thus, at higher flow rates the probability of capturing a given sized particle by diffusional interception diminishes. The effect of air velocity on the inertial impaction mechanism is less pronounced, particularly in the case of tighter membrane filters, because inertial impaction is overshadowed by more efficient size exclusion (Liu et al., 1985; Grant, 1988). The net effect is a shift of the MPPS as a function of air velocity. Such information has to be taken into consideration in order to achieve the desired retention character-

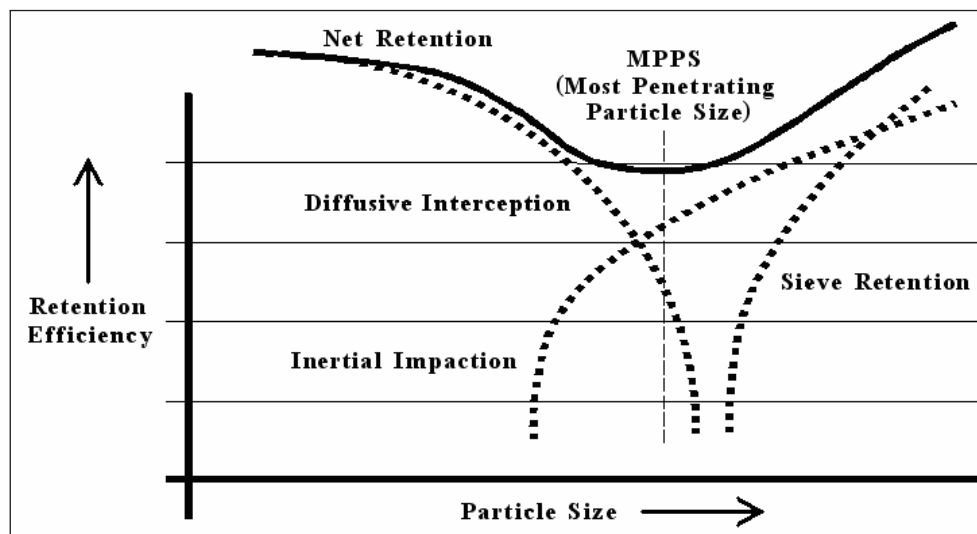


Figure 4: Effect of Various Retention Mechanisms of Particles Retained from a Gas Stream as a Function of Particle Size

istics from a dry gas stream. Additional information on the theory of retention mechanisms is given in Appendix A.

3.4 Factors that Affect the Retention Efficiency

As discussed above, the most reliable mechanism of particle retention from a gas stream by membrane filters is size exclusion because the retention efficiency remains relatively unaffected by the use conditions imposed on the filtration process. This mechanism hinges mainly on the size of the contaminant to be retained in relation to the actual pore size of the membrane in question.

True pore size must not be confused with the nominal micron rating commonly assigned by filter manufacturers to the various types of filters offered. Such nomenclature is intended mainly for labeling purposes. However, due to the lack of uniformity in the rating from one manufacturer to another or due to different filter materials used, even from the same manufacturer, it is generally not advisable to select a filter for a given application based solely on the numerical micrometer rating. Since different retention mechanisms are involved in sterile gas filtration, a numerical pore size rating has even less meaning than it has in liquid filtration. Most manufacturers designate microbial retentive hydrophobic gas filters as 0.2 micron as a reference to “sterilizing” filtration of liquids. These membranes are, in fact, much more efficient in retention in dry gas streams (Liu et al., 1985).

Therefore, gas filters are best described by their performance in challenge tests, which are discussed in Section 7. For most applications, the presence of moisture in the form of condensate affects the filtration process adversely, but ways of keeping the filter element dry are discussed for various applications later in this report.

4. FILTER SELECTION AND SYSTEM DESIGN CRITERIA

Selection of a sterilizing gas filter requires consideration of many important issues, ranging from the retention efficiency through physical durability, compatibility with processing conditions, and ultimately the overall economics of the process. The relative importance of the selection criteria will depend strongly on the given application, but for many applications, the following characteristics need to be taken into consideration.

4.1 Retention Capability

In the pharmaceutical industry, hydrophobic membrane filters are useful in many applications. Very stringent retention expectations may be required for some of the more critical applications, while such requirements may not be necessary for others. In broad terms, the retention efficiency requirements can be classified in the following three categories:

The most stringent expectations are for sterile gas applications, where the filtered gas will be in direct contact with sterile final product or critical surfaces of the associated equipment. Examples include the filtration of compressed gases associated with aseptic filling equipment, blanket gas and venting of sterile bulk product holding tanks, and vacuum break applications in lyophilizers and critical autoclaves. Filters selected for such critical applications should be qualified with an appropriate liquid-based bacterial retention challenge test, and must have an appropriate physical integrity test that is correlated to the bacterial retention capability demonstrated in liquid filtration.

Moderately critical applications are those where the filtered gas will not be in direct contact with exposed sterile product or surfaces. Examples include many intermediate processing steps or the air supplied to a fermentation process. For such applications, filters qualified with aerosol-based bacterial challenge tests and with physical integrity tests that are correlated to aerosol retention capability are appropriate.

Applications that only require a reduction in bioburden have less stringent requirements. Because the retention expectation is similar to what is commonly expected from HEPA filters, dispersed oil aerosol challenges are often deemed acceptable to establish the retention capability of filters used in this type of application.

Classification of a given application into any of these groups and the suggested retention validation approach should be given careful consideration. Other applications may have additional or more specific requirements, such as the need for bacteriophage control in sensitive fermentations, or virus retention in critical applications. A number of articles that address the retention of different types of contaminants, including bacteria and phage, under various conditions and for various types of membrane have been published in the technical literature. However, the applicability of such data to a given situation must be carefully evaluated and justified by the filter user on a case-by-case basis.

4.2 Integrity Testing

As dictated by the application, it may be important to be able to verify the integrity of the filter element by means of a non-destructive physical test to assure the desired retention capability. More details and methods are discussed in Section 8 of this technical report.

4.3 Filtration Rate and Throughput

The flow rate of a filter at a given pressure differential depends on a number of factors, including the type of membrane and support materials, the thickness, porosity and pore-size distribution of the media, among others, as well as the retention characteristics.

For a given type of filter, the flow rate increases with the effective filtration area, but not necessarily in linear proportion. The appropriate filter area or number of individual filter elements for a particular sterilizing filtration application can be estimated from the clean gas flow versus differential pressure data, typically presented by the filter manufacturer in graphical or tabular format. An appropriate allowance for the extent of plugging to be tolerated has to be considered in the calculation of the

area necessary to meet the process objectives. It is necessary to consider the pressure drop of the entire system, including any pre-filters and any piping or ducts leading to and emerging from the sterilizing filter holder. Consideration should also be given to any special characteristics of an application, such as a high pump-out rate or steam-in-place requirements.

The throughput of the sterilizing filter can be increased considerably by the use of pre-filters. In addition, the useful life of the filter may not be limited by plugging, but rather by the number of sterilization cycles, the element can withstand before losing physical integrity.

4.4 Materials of Construction

Sterilizing membranes typically are manufactured from polymers such as PTFE, PVDF, polypropylene, or polyethylene. In addition to the membrane, assembled filter elements, particularly pleated filter cartridges, contain upstream and downstream support and drainage materials. Typically, these layers consist of a hydrophobic polypropylene non-woven medium (fleece), and the pleated packs are embedded in polypropylene by a thermal bonding process. Polypropylene is also a popular material for other cartridge hardware components, including the external cage, the inner support core, and the end caps. Some filter core elements and O-ring adaptors are reinforced with stainless steel or other materials to enhance the durability of the cartridge. Various O-ring materials are also available to suit the needs of a given application. The materials of construction have an impact on several key properties of the assembled filter element, such as thermal resistance, chemical compatibility and resistance to oxidation, and mechanical properties. The filter user should assess their suitability for a particular application.

4.4.1 Hydrophobicity

In order to reduce the potential for blockage by moisture accumulating within the filter element, particularly within the pore structure of the membrane, the materials of construction should be hydrophobic. Hydrophobicity is a reflection of the surface energy of the material compared to the cohesive energy of the liquid. Water, with a surface tension of 72 dynes/cm, is commonly the reference liquid. If the cohesive force exceeds the adhesive force, water will “bead up” rather than spontaneously wetting the surface, as shown in Figure 5.

The degree of hydrophobicity of a material can be expressed as the minimum surface tension of the liquid at which spontaneous wetting occurs, namely, the critical surface tension. Of the popular materials mentioned, PTFE is the most hydrophobic and polyethylene the least,

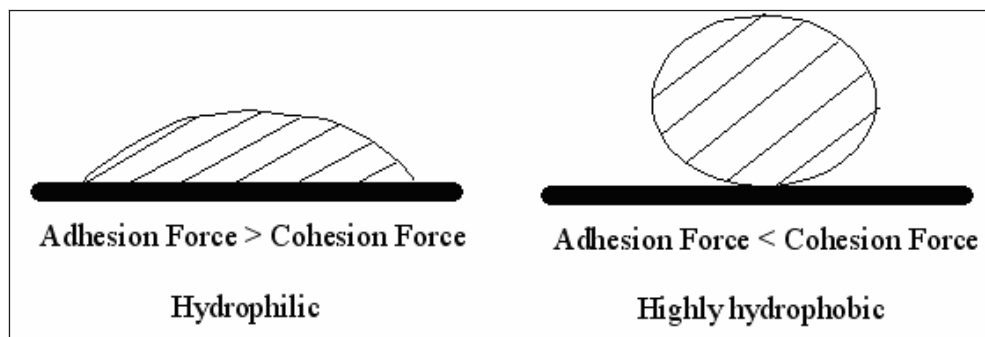


Figure 5: Interaction of Water with Hydrophilic and Hydrophobic Surfaces

as can be seen from the critical surface tension values listed below.

Polymer	Critical Surface Tension (dynes/cm)
PTFE	18
PVDF	25
Polypropylene	29.5
Polyethylene	32

4.4.2 Durability

The filter element has to be able to withstand the rigors of the intended application. Filter manufacturers typically provide information on the materials of construction and on the differential pressure limits that the filter element will withstand. Total inlet and differential pressure limits across the element are typically specified as a function of temperature and the direction of flow. Users must choose the filters in accordance with the needs of their particular processing requirements and must operate the filters within the specified limits to avoid loss of filter integrity and the associated reduction in retention capability. Loss of integrity can also be the consequence of degradation when filtering oxidative gases at elevated temperatures, particularly in long-term use. For such applications, the appropriate materials of construction must be selected or the filter change-out frequency should be adjusted to suit the materials.

Durability is particularly important in steam sterilization of the filter elements. In fact, the economics of some applications hinges on the number of steam sterilization cycles a given filter element can withstand without losing integrity. Sterilization of filter elements is discussed in more detail below.

4.4.3 Toxicity

It is important to assure that the filter system does not release toxic components into the process stream. Although extractables in liquids are of general concern,

extractables cannot be generated in the absence of a solvent and hence are not a concern in dry gas applications. However, most elements should be and are generally constructed of materials that are not toxic based on standard toxicity test methods. These tests involve a static soak of the filter components in various solvents, followed by evaluation of the extracts and the plastic components themselves either in animal models and/or in mammalian cell culture tests. These tests are performed to ensure that filter membrane and support materials do not adversely affect the safety of the product. Filter suppliers typically provide toxicity data according to the standard United States Pharmacopeia (USP) Biological Reactivity Tests, *In Vivo*, for Class VI Plastics.

4.4.4 Particle Shedding

Particle shedding needs to be minimal for some applications, such as the filtration of compressed gases in conjunction with aseptic filling lines and breaking the vacuum at the end of freeze-drying cycles. On the other hand, it may be of little consequence in other processes, such as filtration of the air supply to a fermentor or filtration of the off-gas for such processes. Considering that all filters may shed particles, the possibility of media migration should be considered and assessed for those applications where it is deemed of importance (Decedue and Unruh, 1984; Hall, 1984; Meltzer, 1987a). Particle shedding can be evaluated using a liquid, where the higher viscosity of the liquid is considered to provide a more stringent test condition.

4.4.5 Gas/Filter Compatibility

Incompatibilities between the filter and the process are related to temperature, pressure, oxidation, or a combination of these factors. Excessive temperatures can result in deformation of components, while cryogenic temperatures can cause brittleness and stress fractures. Either extreme can potentially lead to loss of integrity. Oxidative gases, depending on temperature, concentration, and time in service (under flow conditions), can cause surface decomposition and particle generation from

susceptible support components long before there is any loss of integrity.

Due to flammability issues, polypropylene hardware filters should not be used in pure oxygen service. PTFE membrane filters with all-fluoropolymer materials of construction may be suitable for such severe conditions; however, if a sterile gas is required, users should verify that the filter is qualified as a sterilizing grade filter, as this may not always be the case.

4.5 Water Blockage

In many applications, the gas filter may come in direct contact with water or aqueous product solutions. Furthermore, condensation of water vapor can occur within the filtration system. Accumulation of water within the filter element will block the flow of gas, thus interfering with filter performance. The accumulation of water will also promote bacterial and fungal growth, and it should be avoided in all sterile gas applications (Meltzer, 1996; Rowe et al., 1996). Constructing gas filter elements from hydrophobic materials, as discussed above, reduces these adverse effects.

Even the most hydrophobic of filters can end up liquid-logged under some circumstances, particularly during steaming and integrity testing. This will invariably affect the flow characteristics in an adverse manner. The time that is required to dry the filter sufficiently to restore a useable or minimum required flow rate is referred to as the blow-down time. The more hydrophobic the filter media is, the shorter the blow-down time, provided that the filter assembly is properly oriented, with the outlet end pointed downward. For example, one vendor recom-

mends that flushing with a minimum of 75 cubic feet of air (with dew point below 40 °C) per square feet of filter area be used as a rule of thumb for drying hydrophobic filters. Blow-down conditions and times required will vary for different conditions, filter materials, and air/gas dew points.

4.6 Design Considerations for Condensation Control

Accumulation of water within the filter element or the housing will also block the flow of gas, but this can be reduced by an appropriate system design that allows for drainage from the housing and the filter core. The amount of water droplets that reach the housing can be minimized by the use of coalescing pre-filters. The accumulation of moisture within the filter housing can be reduced by opening the lower housing vent. Accumulation of moisture within the filter membrane can be addressed by keeping the filter system at a higher temperature (typically 3–5 °C above) relative to the process temperature.

Potential solutions to the problem include selecting a filter housing that is steam-jacketed or fitted with an electric heat tracer or insulating the housing and associated piping. Properly designed systems eliminate condensate from the filter assembly before it can accumulate (see Figure 6). Such systems must be thoroughly tested, as any blockage could be catastrophic to non-vacuum rated tanks and to the filter element itself.

When using steam-jacketed or heat-traced housings, it should be noted that many materials of construction (e.g., polypropylene cage, core, and membrane support layers) are susceptible to oxidation under extended periods of use at elevated temperatures (>80 °C). The high temper-

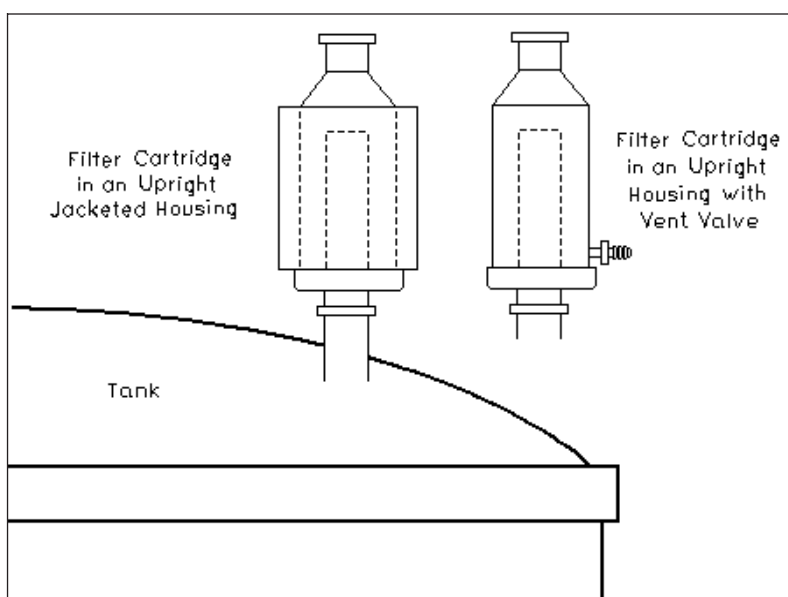


Figure 6: Examples with Filter Oriented for Drainage of Condensate with Steam Jacket or Open Lower Vent Valve

ature experienced in heated filter housings combined with high airflow can accelerate damage to oxidizable (polypropylene) filter components. It is best to avoid elevated temperatures above that recommended by the filter manufacturer, and it should be noted that specifications from many manufacturers will state a lower service life at elevated temperatures. For severe applications, oxidation-resistant materials (such as specially formulated polypropylene hardware and polyaramid support layers) are available.

5. EXAMPLES OF SPECIFIC APPLICATIONS

Most applications for hydrophobic membrane filters can be satisfied with a filter that meets as many of the following ideal characteristics as possible:

- The filter must retain microorganisms, even under adverse conditions such as high humidity.
- The filter should have high thermal and mechanical resistance, sufficient to endure long-term applications under demanding use conditions.
- The filter should withstand multiple steam sterilization cycles.
- The filter should allow high gas flow rates at low differential pressures.
- The membrane should be hydrophobic to resist blockage by condensate.
- The filter construction should be optimized for long, dependable service life.
- The filter must not release fibers.
- The filter must be integrity testable with a test correlated to removal efficiency.
- The filter should be easy to install and maintain.
- The filter's materials of construction should be compatible with the proposed application (e.g., oxygen service)

The relative importance or need for such properties can best be illustrated by a few sample applications.

5.1 Product Contact Gases

The broadest, most critical use of sterilizing grade hydrophobic membrane filters is for gases that are in direct contact with pharmaceutical products. For example, nitrogen gas is widely used to blanket oxygen-sensitive

solutions to reduce degradation. Any gas that comes in contact with solutions should be sterile to maintain low bioburden in terminally sterilized products or to maintain sterility in aseptically filled products. This includes process gases used in tanks or headspace gases used to flush product vials and ampoules.

Due to the critical nature of these applications, hydrophobic membrane filters that are validated to a rigorous liquid-based microbial retention challenge are recommended. In many critical applications, redundant filters in series are frequently employed, but not required. Filters must be routinely integrity-tested in use to assure their efficacy. Membrane materials should be chosen to reflect the conditions of use, especially if filter units are steamed- or sterilized-in-place.

5.2 Fermentor Inlet Air

The volume of air required to maintain the fermentation process depends on the process and the volume of the culture, and filtration systems should be sized accordingly. In large fermentor applications, the air supply may be millions of cubic meters per year and require large filter assemblies. The air supply needs to be reliable to provide proper oxygenation of the culture and sterile in order to avoid costly contamination problems in the process. Filters used in fermentation processes should meet high microbial retention standards and provide high flow rates at a relatively low pressure drop (1–5 psig). Membrane materials for such applications should be hydrophobic, of high void volume, yet show reliable microbial retention capability. Construction of the filter cartridges is optimized to avoid water blockage. The elements also require a high thermal and mechanical stability, because for the process to be economical, they have to withstand many sterilization cycles at elevated temperatures.

5.3 Fermentor Off-Gas

Membrane filters are employed increasingly for fermentor off-gas applications. The challenges in this application are the high moisture content and the high level of microbial contamination of the fermentor exhaust gases. As the gas stream cools, condensation occurs. This, in turn, can result in an undesirable increase of the head pressure within the fermentor. As indicated above in Section 4.6, water blockage can be avoided by choosing the proper design, protecting the final filter with coalescing pre-filters, and heat tracing the filter housings to avoid condensation (Keay, 1991; Orchard, 1991). Off-gas systems should be designed to prevent condensate and coalesced aerosols from reaching the filter. This is often accomplished by having the off-gas condensate drain back into the fermentor.

Also, there is a potential for foam to be carried over into the off-gas, which can lead to blockage of the filter. Therefore, systems should be designed and operated to avoid foaming. Foaming is typically reduced with addition of anti-foam agents or modification of the fermentation media. In difficult processes, it may be necessary to install a mechanical separator to eliminate foam and the potential for filter blockage.

5.4 Vent Filters on Compensial Water and Product Holding Tanks

When liquid is added to or drawn from a tank, an equivalent volume of air is displaced from or into the tank. To avoid bacterial contamination of the contents in critical applications, the air has to be filtered through a sterilizing grade vent filter. The same is true when a holding or transport tank is steam-sterilized because the air that enters the tank at the end of the sterilization cycle has to be sterile. In addition to the rigor of the steam cycle, another challenge presented by this application is blockage of flow due to entrapment of moisture within the membrane.

The need to avoid blockage of flow through the vent filter is particularly important at the end of a steaming cycle. As the tank cools, condensation of steam creates a vacuum that can be estimated from the ideal gas law or steam tables (Cole, 1977; Meltzer, 1987b). At 100 °C, for instance, each liter of steam that condenses will occupy only about 0.6 mL, an almost 1700-fold decrease in volume. Because the bulk of the condensation will take place rapidly, the vent filter should be properly sized to deliver the equivalent of the tank volume of air in a small period of time. If no appropriate measures are taken to prevent the disruption of airflow through the vent filter, the resulting vacuum in the tank may damage the tank. The issue is less problematic in tanks that are vacuum-rated, a feature that makes them considerably more expensive.

Other design features can also prevent tank implosion. For instance, the vent filter can be connected to a source of compressed air, at a pressure high enough to displace the moisture lodged within the pore structure. The preventive measures cited above (in Section 4.6), such as heat-traced housings, should be seriously considered. Special care needs to be exercised in the sizing of the filter to avoid the problems associated with blockage in this application. It is also prudent to fit sealed tanks with a suitable rupture/implosion disc. However, reliance on this feature risks product loss and implies a significant amount of downtime to replace the disc, as well as repeating the cleaning and steaming process.

5.5 Lyophilizer and Autoclave Vacuum Break

The air (gas) that enters the chamber of a lyophilizer will come into direct contact with the sterile product. Likewise, the air that enters an autoclave will come in contact with sterile commodities or equipment. Hence, the gas supplied to reduce/break the vacuum at the end of the lyophilization/autoclave cycle must be sterile in these cases. Disruption of airflow due to condensation can adversely affect the operation, and appropriate measures to prevent this should be taken. The filter element in such applications needs to be sterilized, most often by steaming in place. The filter manufacturer's recommendations for steaming or sterilization should be adhered to, particularly if steaming in the reverse direction is required. Because the filter may be subjected to repeated steaming or sterilization cycles in such applications, it should be durable, and should be integrity-tested on a regular basis to assure the expected microbial retention level (see Section 8.5 for considerations for integrity test practices). Ease of integrity testing, placement of the filter, and easy access to the filter are critical in this application.

5.6 Gas Used for Drying and Transfer/Fill Line

Some components (such as rubber stoppers) and large equipment (such as holding tanks) are typically rinsed in water for injection and dried after steaming. Drying is especially critical if they are to be used in oil-based sterile product formulations. Often, compressed air is used to accelerate the drying process.

In addition, in many processes, the sterile bulk product must be transferred from the sterile holding tank to the filling line. This is often accomplished by pressurizing the head space in the holding tank with a suitable gas.

The gas in such critical applications must be sterile and free of particles, and a suitable filter must be chosen. Filters in such applications should be routinely sterilized and integrity-tested to assure the expected microbial retention capability.

5.7 Blow-Fill-Seal Equipment

Large amounts of sterile compressed air are needed to run blow-fill-seal operations. Often, the equipment is fitted with several different air filtration systems in order to provide sterile air to individual process steps, such as in molding the primary container or shielding critical portions of the machine to prevent the ingress of environmental air containing bacteria and particulate matter. The filtered air contacts critical surfaces as well as the product during the filling step; thus, a high level of bacteria retention must be assured through proper filter se-