Fluid Sterilization by Filtration

Third Edition

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Preface

The first edition of this book, published in 1992 by Interpharm Press with a different subtitle, evolved from talks I made before a 1991 meeting of the Parenteral Drug Association. Theodore Meltzer, chair of that meeting, and editor of the massive *Filtration in the Pharmaceutical Industry,* published by Marcel Dekker in 1986, graciously introduced me to Interpharm.

From 1977 to 1992, I chaired an American Society for Testing and Materials (ASTM) subcommittee on liquid filtration. We wrote about 15 filtration test methods. During 1986, ASTM sponsored a symposium on filtration and published the proceedings in *Special Technical Publication (STP) 975*, in two volumes, one on gas filtration, the other on liquid filtration. Ted Meltzer then introduced me to Tall Oaks Publishing, who, in 1990, brought out my *Fundamentals of Fluid Filtration, a Technical Primer.*

In 1992, the American Filtration and Separation Society (AFS), looking beyond ASTM methods, put out a call for test methods. I collected those methods and other methods and wrote *A Survey of Test Methods in Fluid Filtration,* which was published in 1995 by Gulf Publishing Co. After that press run sold out, Gulf declined to publish an updated second edition. With Gulf's permission, I used information in *Survey* to write a 1998 second edition of *Fundamentals*, which was published in 1998.

In 2001 Mark Jornitz and Ted Meltzer wrote *Sterile Filtration: A Practical Approach,* published by Marcel Dekker. While that work does indeed cover information newer than Meltzer's 1987 book, there are matters that are not included in it that I believe are important for a thorough understanding of the subject. Meanwhile, CRC Press had acquired Interpharm. CRC agreed to publish the present book, the third edition of my *Fluid Sterilization by Filtration*.

The Author

Peter R. Johnston, P.E. was trained in chemistry. After a 1952 Army combat tour in Korea as a platoon leader, he began doing R&D work in the chemical process industry and obtained patents in three different fields of chemistry.

In 1972 his work led him into the filtration business. He became a charter member of ASTM's Committee 21 on Filtration, and for 15 years he chaired the subcommittee on liquid filtration, guiding that group into writing about 15 test methods. ASTM elected him a Fellow.

Johnston has published more than three dozen papers on filtration in a variety of journals and has spoken at many technical meetings. He retired from industry in 1992 and now consults with a variety of people on questions about filtration. He continues to write papers on the subject and reviews papers for publication.

Introduction

A membrane filter medium, meant to sterilize a clear or nearly particle free pharmaceutical liquid, is employed in the final filtration step, just before the operation of filling vials or bottles. But, before that final filtration step, the liquid has already undergone previous filtration with ordinary fibrous filter media. Such previous steps reduce any debris that would quickly clog a membrane filter. Thus, while this book aims at the final filtration step it also addresses the general subject of filtration. Indeed, in some cases that will be discussed, the product to be recovered from a liquid suspension is a powder.

Materials of Construction

When selecting a filter medium, the first thing to consider is the material of construction. The medium must stand up to the fluid to be filtered. Suppliers of membrane filters provide lists of fluids that can be used with each of their products and point out fluids that must not be used with some. Furthermore, suppliers will gladly test any special fluid for compatibility.

The Integrity Test

In the pharmaceutical industry, regulations require that a membrane filter medium meant to sterilize a stream be tested for integrity before and after filtration, to make sure no fluid will or has leaked around it. The integrity test is sometimes called the diffusive flow test, the forward-flow test, the pressure hold test, or the flow decay test. It is performed with the bubble-point test. Instruments are commercially available to perform such tests, along with directions for performing them. By following these procedures and recording the results, operators fulfill the requirements of good manufacturing procedures.

Yet beyond merely following procedures, the alert operator will understand what the procedures and instruments actually measure and do not measure and what the results actually mean. Furthermore, to avoid being misled, the alert investigator will understand the method by which any instrument he or she uses derives results from measurements.

Pore Size

The results of bubble-point tests point to the size of the largest pores. Yet, there is ambiguity in this method, which has yet to be standardized. One investigator's largest pore differs from another's. Similarly, one investigator's absolute filtration differs from another's.

Since the largest pores carry only a very small fraction of the stream, a more important measure of pore size is the flow-averaged diameter, defined by a fluid during flow through the medium. The largest pores on the surface do not extend into the depth of the medium. Yet, when the bubble-point test is correctly performed, it does give an indication of the diameter of the flow-averaged pore. That is, in the random array of pore sizes, the largest pore on the surface is about three times the diameter of the flow-averaged pore.

The flow-averaged pore size is larger than the volume-averaged pore size, which is larger than the number-averaged pore size. Yet, filtration efficiency, while related to pore size, is also related to the thickness of the filter and to the internal surface area, among many other variables.

Rated Pore Size

Aside from pore size, distribution of pore sizes, and the thickness of the filter membrane, the drug manufacturer simply wants a membrane to stop a certain sized microbe. Hence, membranes are rated by a somewhat standardized test that determines if a specific test microbe is stopped with great efficiency. When it does, the membrane is rated for that microbe. Thus, writers employ correct terminology when they speak of, say, a 0.45-μm rated membrane. The rating does not mean the membrane has a pore diameter, whatever that means, of 0.45 μm.

The 0.45-μm rating indicates a membrane stops *Serratia marcescens* with great efficiency. That is, when feeding 10^7 microbes per square centimeter of membrane surface, less than one such microbe appears in the filtrate. Such membranes were once used for sterilizing filtration, but it was found that some filtrates were not sterile. The microbe passing was cultured as *Pseudomonas diminuta* and then used to rate membranes as 0.20 μm (or 0.22 μm, as if the difference is significant). This rating was apparently assigned to show that such a membrane has half the rating of 0.45 μm, even though *Pseudomonas diminuta* (now called *Brevundimonas diminuta*), so cultured, is actually $^4/_5$ the diameter of *Serratia marcescens*. The viscous flow-averaged pore diameter of a 0.45-μm-rated membrane is near 0.85 μm. The viscous flow-averaged pore diameter of a 0.20-μm-rated membrane is near 0.55 μm.

Compared to suppliers of paper and other nonwoven fibrous filter media, suppliers of membrane filters are straightforward in reporting fundamental facts about their membranes. They report thickness, porosity (ratio of void volume to bulk volume), and the flow rate of water under a given driving pressure. From such data, we can deduce the permeability and, thus, the flow-averaged pore diameter. Since most membrane filters are of equal thickness, filtration efficiency is then a simple function of the flow-averaged pore diameter. But filtration efficiency varies with changing membrane materials, as well as with changing fluid-flow rate, viscosity, temperature, and properties of the microbes and particles to be separated.

Someday, perhaps, suppliers of fibrous filter media will report such fundamental data.They generally do report thickness, as caliper, but they fail to report porosity, and they often fail to report the driving pressure for a fluid-flow rate they call permeability. In classifying grades of filter media all of the same material of construction, we look to each for the flow-averaged pore diameter and the thickness.

Capacity of a Filter Medium

The capacity of a filter medium is the volume of a stream that can be fed to a unit area before the resistance climbs by a factor of, say, 10. That is, with a constant fluid-driving pressure, capacity refers to the time before the flow rate falls to, say, $1/10$ of the initial rate. Or, with constant-flow filtration, capacity is the volume filtered before the driving pressure must be increased to, say, 10 times greater than the starting pressure.

In either case, we measure the rate at which the medium loses permeability. Empirical filtration laws point to four different mathematical statements that describe rate losses. Identifying which law one encounters provides additional understanding of the mechanism of filtration. Ideally, we want to see cake filtration, where solids are retained on the surface of the medium. That is, the increasing resistance to flow is due only to the increasing thickness of the cake of collected solids. The pores of the filter are not plugged.

The area of the filter medium required for the filtration job at hand depends, of course, on the volumetric flow rate and the viscosity of the process stream and whether we have a batch or continuous stream. In the latter case, we must decide how often we want to install a fresh filter. More specifically, we must consider the velocity of the stream approaching the face of the medium. It is a direct function of the fluid-driving pressure, the difference in pressure between the upstream face and the downstream face. Obviously, we do not want an undue amount of pressure for fear of rupturing the membrane or rushing the fluid through the membrane so fast that microbes or particles will squeeze through the pores.

Configurations of Membrane Filters

Filtration devices fall into two general types, each type consisting of housing with a replaceable filter medium. One type of housing holds a flat-sheet, 293-mm-diameter membrane or perhaps a stack of such membranes. On a smaller scale, discs are available with diameters as small as 13 mm, along with housings to hold them.

One type of housing is designed to hold cylindrical cartridges, which come in various diameters and lengths, typically about 6.4 cm (2.5 in.) in diameter by 25 cm (10 in.). Each cartridge contains a membrane that is pleated so that a large membrane area — 4000 cm^2 for the 10-inch cartridge — is contained in a relatively small space. Different sized housings hold different numbers of cartridges. Some cartridges contain bundles of hollow fibers, the walls of which constitute the filter medium.

Cross-Flow Filtration

When particles or gels in a stream could quickly clog a membrane, the feed stream is passed across the membrane at high velocity so that solids suspended above the membrane are swept away while clear fluid passes through. The stream flowing across the top of the membrane, called the concentrate, may be returned to the feed tank.

Fibrous Filter Media

Felts of asbestos fibers were formally used as sterilizing filters; one company offered potassium titanate fibers mixed with resin-bound cellulose fibers. Such filters are no longer used as final filters for fear that some fibers may appear in the filtrate. The day may come when small-diameter but long fibers, like the new nanofibers, are used to build a mat that does not release fibers. But until then, fibrous media are only used to prefilter liquids that, in the end, are sterilized and made fiber free by passing through a membrane.

Mats of ordinary-diameter fibers are useful, though, in sterilizing gas streams without release of fibers into the filtrate. Particles and microbes are more easily separated from a gas than from a liquid because of the lower viscosity of gasses. But fibrous media that sterilize gas streams lack small enough pores to pass a bubble-point test. All we have for testing the integrity of a fibrous gas filter is a measure of the gas flow vs. driving pressure. The

manufacturer demonstrates that such a filter can stop of cloud of airborne particles or droplets with small diameters. Such filters are employed to clean air fed to fermenters.

The Vent Filter

To be really sure that a gas is sterile, membranes are used. The vent filter cartridge, placed above a tank of liquid, is composed of a hydrophobic membrane. The cartridge allows sterile air to breath into or out of the vessel as the volume of liquid changes, so that the vessel will neither rupture from high pressure nor collapse from low pressure. Because the pores in the vent filter must be small enough to prevent the passage of microbes, water vapor cannot be allowed to condense in the pores. If water vapor did condense there, the differential pressure across the membrane required to blow water from the pores and let air through would be greater than the differential pressure we could allow across the vessel. So a steam jacket is used to keep the vent filter warm enough to prevent condensation.

To determine the area of the membrane surface required for a vent filter, that is, the volumetric flow of air that it must serve, consider the volumetric flow rate of the liquid that will enter or exit the vessel. Thus, before installing a vent cartridge of a certain size or two or more cartridges, look at the specifications around such cartridges in terms of the volumetric flow rate of air it can best handle. As a safety feature, the vessel will be fitted with a pressure-rupture disc.

Gas Filter vs. Liquid Filter

As a rule, a liquid filter meant for sterilization must not be in service for more than one 8-hour shift because a single microbe might pass through the membrane and develop into a colony on the downstream face. If a liquid filter is to be used again for another run, it must be resterilized and retested for integrity. However, during the first run, the membrane may collect enough particles and organic debris to plug some of the pores, in which case the cartridge must be discarded. A vent filter, on the other hand, handles a relatively clean stream; thus, the pores do not readily plug with debris. And a vent filter can be repeatedly steam sterilized and reused. In the manufacturing of antibiotics, vent filters atop fermentation tanks are resteamed as many as 50 times between runs (Meltzer 1987).

The integrity test cannot be performed while the vent filter cartridge is in the process housing. The cartridge must be separately tested in test housing.

The hydrophobic vent cartridge should be soaked in a solution of 50% isopropanol in water to wet and fill the pores. Then follow the pressure hold test and the bubble-point test, understanding that the bubble point is a function of the surface tension of the liquid in the pores. Since isopropanol has a lower surface tension than water, the required bubble-point value (pressure) with the alcohol solution is lower than with pure water. After the cartridge passes these tests, place it in an autoclave to sterilize it and drive off the liquid. Then aseptically place it in the vent housing. The housing has already been sterilized.

Alternatively, a hydrophobic cartridge may be tested for integrity by forcing water against the dry membrane, without having to bother with the alcohol. If a high enough pressure of water is required to force the first flow of water through the largest pores, the cartridge passes the integrity test. But this test has yet to become standard.

In the case of liquid filters, the pressure hold test and the bubble-point test are performed in place. That is, after the cartridge is installed in the housing and the assembly is sterilized, some of the liquid to be filtered is run through to fill the pores of the membranes. Downstream from the filter, plumbing is provided so that this first liquid can be discarded or recycled in case the filter fails the integrity test.

Units of Measure

Before the trend of describing units of measure in SI units, writers, in presenting their findings and examples, have employed a wide variety of units (especially with pressure). The following list offers conversion units relevant to subjects in this book.

Pressure

$N/m^2 = Pa$ (N = Newton, Pa = Pascal)

1 lbf/in^2 = 1 psi = 6.895 kPa = 144 lbf/ft^2

1 mm Hg = 133 Pa = 1 torr

1 cm Hg = 1.333 kPa

1 inch water = 249 Pa

1 atm = $1.013 \cdot 10^5$ Pa = $1.013 \cdot 10^6$ Baryes, or dyn/cm^2 = 14.7 psi

1 bar = 10^6 Baryes = 0.9869 atm

Viscosity

$$1 \text{ centipoise (cP)} = 10^{-3} \text{ N}\cdot\text{s}/\text{m}^2 = 10^{-3} \text{ Pa}\cdot\text{s}$$
$$= 10^{-3} \text{ kg}/\text{m}\cdot\text{s} = 2.89 \text{ lbf}\cdot\text{sec}/\text{ft}^2$$

$$\nu = \eta/\rho = 0.22t - 180/t$$

where

ν = kinematic viscosity, centistokes
η = absolute viscosity, centipoise
ρ = density, specific gravity
t = Saybolt Universal, seconds

Density

1 g/cc = 1 Sp.gr. = 62.43 lbm/ft^3 = 8.34 lbm/U.S. gal
= 1 kg/liter = 10^3 kg/m^3
°Bé = 145 – (145/Sp.gr), for Sp.gr. greater than 1.0.
= (140/Sp.gr.) – 130, for Sp.gr. of 1.0 and less.
API = (141.5/Sp.gr.) – 131.5

Surface Tension

1 dyn/cm = 10^{-3}N/m

Volumetric Flow Rate

1 U.S. gal/min = $6.31 \cdot 10^{-5} m^3/s$
1 liter/min = $1.67 \cdot 10^{-5}$ m^3/s
1 ft^3/min = $4.72 \cdot 10^{-5}$ m^3/s

Area

1 in^2 = $6.45 \cdot 10^{-4}$ m^2
1 ft^2 = $9.29 \cdot 10^{-2}$ m^2
1 cm^2 = 10^{-4} m^2

Prefixes

M = mega, 10^6
k = kilo, 10^3