Global Academic Journal of Pharmacy and Drug Research

Available online at https://www.gajrc.com
DOI: 10.36348/gajpdr.2022.v04i04.002

OPEN ACCESS

ISSN (P): 2706-9044
ISSN (O): 2707-255X

Review Article

Filter Integrity Test for Aseptic Processing

Prashant Khemariya[1*], Dr. Ankit Agrawal[2], Dr. Elango Minnoor[3]
[1]PhD Scholar, Rabindranath Tagore University, Chiklod Road, Bhopal 464993, Madhya Pradesh, India
[2]Head, Department of Life Science, Rabindranath Tagore University, Chiklod Road, Bhopal 464993, Madhya Pradesh, India
[3]Associated Vice President, Biocon Biologics Limited, Electronics City, Phase – II, Hosur Road Bengaluru 560100, Karnataka, India

***Corresponding Author**
Prashant Khemariya
PhD Scholar, Rabindranath Tagore University, Chiklod Road, Bhopal 464993, Madhya Pradesh, India

Article History
Received: 14.08.2022
Accepted: 19.09.2022
Published: 23.09.2022

Abstract: The sterile manufacturing process using sterilizing grade membrane filtration has been practiced reliably and safely over the years. However, to prove its reliability and safety, the integrity of the filter must be tested. Typically, filter integrity testing is performed prior to assembling and using the filter unit. Sterilizing grade filtration is an acceptable process only when the integrity of the filter has been tested. This fact is stated in various guidelines that recommend the use of integrity tests before and after filtration. The integrity of the filter assembly should be verified by an appropriate method, such as such as a bubble-point pressure test or a forward-flow pressure test, before and after use. Irregular leakage flow rates should be noted and examined. The results of these filter integrity checks must be entered in a master batch record. Of all the structural features that characterize a filter, none appears to be more relevant to particle retention, whether viable or impervious particles, than its pore size.

Keywords: Aseptic processing, sterile manufacturing, filter validation, filter integrity.

INTRODUCTION

Integrity means the quality of being honest and the history of filter integrity testing started in the mid of 1970s and since then the process and parameters have undergone significant changes because of industrial need enhancement of product quality and patient safety and finally to reduce the risk to the life. The tests used to carry out to verify and assure the quality and readiness of the filter membrane regarding the regulatory requirements are called filter integrity tests. The instrument which performs this task is called filter integrity machine or instrument. In the 1970s filter integrity testing was performed by just a manual bubble point test only for a few critical use filters, using a pressure gauge. In 1987, both FDA European Good Manufacturing Practice (GMP) (regulators) have introduced guidance to the industry of mandatory integrity testing of critical use filters accelerated the need for high performance automated test equipment.

During 1990-98, recommendations for filter integrity testing by the regulatory bodies had expanded. The EU Guidelines to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use, Annex 1 (Manufacture of Sterile Medicinal Products) or "Annex 1" has introduced the requirement for verifying the integrity of a sterilizing grade filter before application and after its sterilization [PUPSIT- pre-use and post-sterilization]. The requirement was unchanged in the EU guidance 2008 revision and in the 2017 draft revision to Annex 1. This requirement was not

mandatory by the U.S. FDA, EMA inspectors and some PIC/S inspectors have been increasingly expressing expectations for companies to employ this testing procedure. Till now 40 years after the subject that still generates some technical discussion.

Industry must follow current good manufacturing practice (CGMP), aseptic processing regulations (21 CFR parts 210 and 211) if manufacturing sterile drug and biological products using. There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization.

Terminal sterilization usually involves filling and sealing product containers under high-quality environmental conditions. Products are filled and sealed in this type of environment to minimize the microbial and particulate content of the in-process product and to help ensure that the subsequent sterilization process is successful. In most cases, the product, container, and closure have low bioburden, but they are not sterile. The product in its final container is then subjected to a sterilization process such as heat or irradiation.

In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together. Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment. Aseptic processing involves more variables than terminal sterilization. Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes. For example, glass containers are subjected to dry heat; rubber closures are subjected to moist heat; and liquid dosage forms are subjected to filtration. A terminally sterilized drug product, on the other hand, undergoes final sterilization in a sealed container, thus limiting the possibility of error.

Sterile filters are key components during aseptic production of drugs and drug products (solutions such as large volume parenteral (LVPs) and small volume parenteral (SVPs). The fundamental function of these filters to retain germs (Viable Particles) and Non-Viable particles from gasses and liquids to avoid contamination the manufactured product. According to the regulatory requirement every drug and drug product manufacturers are mandate to test the filter for its integrity before and after every production cycle. By execution of filter integrity test, it's demonstrated that the filter is fully functional and that no unwanted components did pass through it.

Consistently validated performance of the filter is very important and maintaining the controlled performance of the filter is one of the most important and challenging process parameters. There are several unusual complications in the aseptic pharmaceutical process which affect Integration of a filter. Factors which can cause wear to the filter elements- as particle load, fluctuations in pressure and temperature, and cleaning steps. In case the test is failed, it shows that the filter is no longer re-usable, and also the previously filtered batch needs inspection. A filter can be damaged due to a number of issues such as irreparable blockage and cracks of the filter membrane or changes to the membrane or pore structure, thereafter blockage can be easily detected during the process run, cracks or changes in pore structure cannot be detected that easily. The method for examination these filter element belongings throughout the process is called the filter integrity test. In practice two classifications of integrity testing are destructive and non-destructive tests.

1. **Destructive Challenge Testing** (as per ASTM F838-83 methodology) is the best way to determine a sterilizing filter's ability to retain bacteria. Bacterial challenge testing provides assurance that the membrane and fabricated device meet the critical performance criteria of a sterilizing filter. The test is performed on a statistical sample of each lot of membrane and fabricated devices produced.

Bacterial retention test, 0.22 µm filter discs and devices are challenged with a solution of culture medium containing bacteria (*Brevundimonas diminuta* ATCC 19146) at a minimum challenge of 10^7 per cm^2. The effluent is then passed through a second 0.45 µm assay filter disc that is placed on an agar plate and incubated.

2. **Non-Destructive Testing-** Non-destructive testing can be performed on the filter before and after use. Filter integrity prior to batch processing prevents the use of a non-integral filter for the batch. Integrity Testing After Batch processing can detect whether the integrity of the filter has been compromised during the process. Detecting a failed filter alerts the operator to a problem immediately after batch processing, eliminating delays and allowing for faster reprocessing.

There are three types of non-destructive testing - the bubble point test, the diffusion test, and the waterflow integrity test for hydrophobic filters.

a. **Bubble Point Test**- The test is simple and cost-efficient. Bubble point test is one of the mostly used non- destructive integrity test methods in the pharmaceutical and Biotech industry. Bubble point is based on the fact that liquid is held in the pores of the filter by surface tension and capillary forces. The process takes advantage of capillary forces as well as surface tension of a liquid applied to the filter. That's why a suitable liquid need to be added to the filter to moisten the filter surface completely before the beginning of the test. This liquid can be water or an alcohol-water- mix, depending on the filter composition. Afterwards, pressure is applied to the filter and increased gradually. If the pressure exceeds a certain value, characteristic bubbles appear on the other side of the filter. This means that the liquid has been pushed through the filter and overcome the capillary forces retaining it. If the pressure is below a certain limit value it's a sign that the filter doesn't work properly anymore. In this case, the filter can't be used in production anymore and has to be replaced. The minimum pressure required to force liquid out of the pores is a measure of the pore diameter.

The bubble point is expressed as -

$$BP = \frac{4 . k . \gamma . \cos \theta}{d}$$

Where
k = shape correction factor
γ = surface tension
θ = contact angle
d = pore diameter

A bubble point value lower than the specification is an indication of one of the following:
- Fluid with different surface tension than the recommended test fluid.
- Integral filter, but wrong pore size.
- High temperature.
- Incompletely wetted membrane.
- Non-integral membrane or seal.

In short - If bubbling appears at a lower pressure than the set pressure, the test is considered a fail. The pressure at which bubbling occurs downstream of the filter is its Bubble Point.

b. **Diffusion Test (Forward Flow Test and Pressure Hold Test) –** The diffusion test takes advantage of the natural diffusion of gas molecules according to Fick's law- At differential gas pressures below the bubble point, gas molecules migrate through the water-filled pores of a wetted membrane. The filter needs to be moistened with a liquid just like in the bubble point test. Afterwards, pressure is applied that equates to roughly 80% of the specified bubble point pressure. The gas molecules diffuse through the water-filled pores of the filter because of the effort to maintain a concentration balance. The higher the pressure and the larger the filter surface, the larger is the diffused gas quantity. The system replaces the gas quantity measured on the side of the filter continually by supplying the same gas quantity on the non-sterile side. This way, the differential pressure is constant during the entire duration of the test and only smaller drops in pressure are measured. In case of the pressure hold test, also known as pressure decay test, the device doesn't supply any further gas.

In short - If the value of the gas flowrate comes higher than the recommendation, the test failed.

A diffusional flow reading higher than the specification is an indication of one of the following:
- Wrong pore size.
- Temperature other than ambient.
- Incompletely wetted membrane.
- Non-integral membrane or seal.
- Liquid/gas combination different than the recommended fluids.
- Inadequate stabilization time.

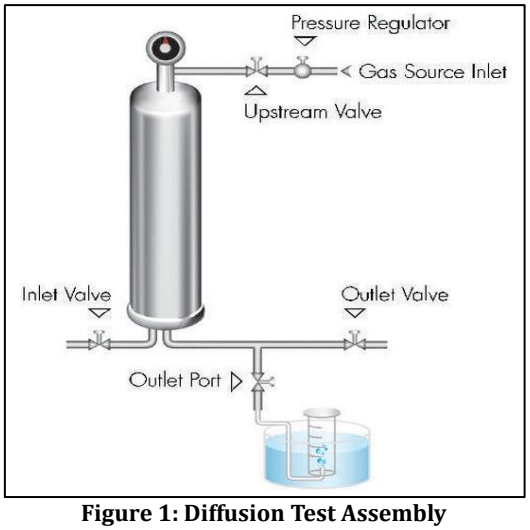

Figure 1: Diffusion Test Assembly

The pressure hold value is dependent on the diffusional flow and upstream volume. It can be calculated using the following equation:

$$\text{Pressure Hold Test Formula} = \frac{D\,(T)\,(Pa)}{Vh} = \Delta P$$

Where:
D = Diffusion rate (mL/min)
T = Time (minutes)
Pa = Atmosphere pressure (1 Atm or 14.7 psi)
Vh = Upstream volume of apparatus (mL)
ΔP = Pressure Drop (bar or psi)

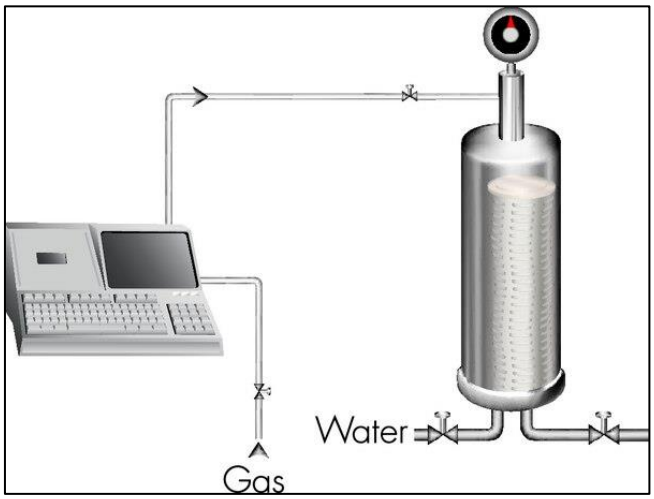

Figure 2: Pressure hold test assembly

c. Water Flow Test - The water flow test is used for hydrophobic filters that are unsuitable for the first two measuring methods due to the nature of the liquid to be used for wetting. The water-repellent characteristics of the filter are taken advantage of instead. Water is applied to the filter during the performance of the test and the pressure is increased. The water enters into the pores of the filter in the so-called intrusion area, but doesn't permeate it because the hydrophobic forces are too strong. The water flow increases exponentially above a certain pressure value and penetrates the filter. The pressure value, measured at the moment the water leaks out, is to be determined and compared to the approved values provided by the filter manufacturer.

Right strategy to evaluate filter performance-

1. **Prior to Installation** – it will ensure that there was no damage while receiving.
2. **After Installation -** it will ensure that the filters are properly installed (no O-ring leaks, etc.) and undamaged.
3. **After in-Line Sterilization** – by using IPA, hot water, steam - to make sure no damage occurred
4. **After Autoclaving** (performed on a filter after removal from its housing) and before re-installation
5. **Pre-Process Operation** (to make sure the filters are undamaged and properly installed)
6. **Post-Process Operation** (to make sure no damage or upsets occurred during processing). This is employed in bio/pharmaceutical operations where sterile product is critical.

The bases of the tolerance data (test results) are validation processes conducted by the manufacturer of filters. These are used to determine tolerances level by correlating absolute, destructive test methods (or bacteria challenge test) with filter integrity tests. Both test methods rely on a procedure of wetting the filter membrane with a pre-defined medium (typically ultrapure water, but also customer-specific liquids)

Automated Filter Testing

Good Manufacturing Practice (GMP) moving towards Good Automated Manufacturing Practice (GAMP), where paper documents (MBR or batch records) migrated to electronic data, concerns over data integrity have been addressed and improved through regulatory guidelines, and increased clarification by the FDA in the form of 21 CFR part 11. Similarly, some test instruments can offer secure data management and data transfer. Automated Filter integrity test machine is demanding which will provide confidence that a static filter integrity test result is a true result that cannot be altered. Effective and compliant data handling can be assured when automated filter integrity test

instruments are designed following ALCOA Plus principles.

According to GMP guidelines, integrity testing equipment is generally rated as Software Category 3 and Hardware Category 1. Testing equipment must be manufactured according to the latest industry standards and designed with components approved by the FDA. They must also have the necessary technical controls for use in environments compliant with 21 CFR Part 11. Integrity Test Equipment is defined as 'off-the-shelf'. A comprehensive verification/qualification package designed by the vendor for such equipment can significantly reduce qualification efforts for the user.

Routine calibration of instrumentation is an integral part of GMP compliance. However, this can easily be overlooked when focusing on the design and working characteristics of an integrity testing device.

Preface

21 CFR 211.113 – Control of microbiological contamination,

(b) Appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes [43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008].

Addresses the validation of aseptic and sterilization processes.

REFERENCES

- Centers for Disease Control and Prevention (CDC. (1998). Clinical sepsis and death in a newborn nursery associated with contaminated parenteral medications--Brazil, 1996. *MMWR. Morbidity and mortality weekly report*, *47*(29), 610-612.
- Cooper and Gunn's. Tutorial Pharmacy by S. J. Carter.
- FDA Guidance for Industry, Sterile Products Produced by Aseptic Processing-Current Good Manufacturing Practice, Part V Personal Training, Qualification, Monitoring, Part B. Filtration Efficacy; 2004 (see D.10 Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice).
- Grandics, P. (2000). Pyrogens in parenteral pharmaceuticals. *Pharmaceutical technology*, *24*(4), 26-35.
- ISO 14644-1: Cleanrooms and Associated Controlled Environments, Classification of Air Cleanliness.
- Ljungqvist, B., & Reinmuller, B. (1997). Cleanroom Design: Minimizing Contamination through Proper Design; *Interpharm Press.*
- Lord, A., & Levchuk, J. W. (1989). Personnel issues in aseptic processing. *Biopharm*, (Sept), 34-40.
- NASA Standard for Cleanroom and Work Stations for Microbially Controlled Environment, Publication NHB 5340.2 (August l967).
- Ph. Eur. Edition 6, Basic Volume 2008, 5.1.1 Methods for manufacturing sterile preparations, p. 769.
- Pikal, M. J., & Dellerman, K. M. (1989). Stability testing of pharmaceuticals by high-sensitivity isothermal calorimetry at 25 C: cephalosporins in the solid and aqueous solution states. *International journal of pharmaceutics*, *50*(3), 233-252.
- Pikal, M. J., Lukes, A. L., & Lang, J. E. (1977). Thermal decomposition of amorphous β-lactam antibacterials. *Journal of Pharmaceutical Sciences*, *66*(9), 1312-1316.
- Pikal, M. J., Lukes, A. L., Lang, J. E., & Gaines, K. (1978). Quantitative crystallinity determinations for β-lactam antibiotics by solution calorimetry: Correlations with stability. *Journal of pharmaceutical sciences*, *67*(6), 767-773.
- Sambamurthy, K. (2007). *Pharmaceutical engineering*. New Age International.
- Subrahman, C. V. S., Setty, J. T., Suresh, S., & Devi, V. K. (2014). *Pharmaceutical engineering: principles and practices*. Vallabh Prakashan.
- Swarbrick, J. (2013). *Encyclopedia of Pharmaceutical Technology: Volume 6*. CRC press.
- Technical Order 00-25-203, Contamination Control of Aerospace Facilities, U.S. Air Force, December l, l972.