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MILLIPORE

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Hydrophilic

DURAPORE

Cartridges and Capsules

User Guide

HOW TO USE THIS GUIDE

The *Hydrophilic Durapore Cartridges and Capsules User Guide* is a reference that operators should find helpful at all stages of product use. This document contains details on supporting background, guidelines, standard operating procedures, and provides references for users to access additional information. The information is provided in chronological order: physical description, handling and installation, sterilization, pre-use integrity testing, sterile filtration, and post-use integrity testing.

Each section begins with supporting background information to help users understand the reasoning behind the recommendations and standard operating procedures (SOPs). If users ever encounter problems, this guide provides information on how to identify and solve them. The guide is designed this way to encourage the user to read the background information before using the filter. It also helps users avoid common pitfalls and make their filter using experience predictable and problem-free. The recommendations and SOPs follow the background information so users can successfully complete any of the filter processes.

Contact Millipore Technical Service at **1-800-MILLIPORE** (1-800-645-5476) if you have any questions or require further information.

Table of Contents

Chapter 4—Pre-Use Integrity Testing of Hydrophilic Durapore Cartridges and Capsules

Chapter 5—Sterile Filtration Using Hydrophilic Durapore Cartridges and Capsules

Appendix A—Maximum Extractables of Hydrophilic Durapore Cartridges and Capsules

Table of Figures

Table of Tables

Chapter 1

Description of Hydrophilic Durapore Cartridges and Capsules

Introduction

This chapter provides information on the physical characteristics of hydrophilic Durapore cartridges and capsules. The physical characteristics of the filters include:

- Materials of construction
- Nominal device dimensions
- Nominal effective filter area
- Maximum extractables
- Maximum oxidizable substances

Definition of a Cartridge and a Capsule


A cartridge is a filter used in a stainless steel housing.


A capsule is a filter in a self-contained, disposable plastic housing.

Hydrophilic Durapore Cartridges

This section outlines the materials of construction, nominal device dimensions, nominal effective filter area, recommended flush volumes (post sterilization), and maximum oxidizable substances of the hydrophilic Durapore cartridge.

Table 1–1: Hydrophilic Durapore Cartridges—Materials of Construction

Device	Item Number (abbreviated)*	Membrane**	Materials: Cage/ Core or Disk	Materials: Membrane Filter	Materials: Support Web	Materials: O-rings
Durapore Cartridges, 5”-30” and Optiseal® Durapore Cartridges	CVGL---- CVDR--PP, CVHL--PP-, CVVL----, LAGL04---, LAHL04PP-, LAVL04---,	Durapore Hydrophilic Membrane	Rigid Polypropylene	Modified Polyvinylidene fluoride (PVDF)	Spun-Bonded Polypropylene	Silicone
Charged Durapore Cartridges and Optiseal Charged Durapore Cartridges	CCGL----, LCGL----,	Durapore Hydrophilic Membrane with positive charge	Rigid Polypropylene	Modified PVDF, with positive charge	Spun-Bonded Polypropylene	Silicone
Durapore 0.65 µm Multimedia Cartridges	CVDR--TP-	Milligard® RW19, 1.2 µm Filter Media Over Durapore Hydrophilic 0.65 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus Mixed Esters of Cellulose (MEC) on a polyester web	Spun-Bonded Polypropylene	Silicone
Durapore 0.45 µm Multimedia Cartridges 10”-30”and Optiseal Multimedia Cartridges w/ Durapore membrane	CVHL--TP-, LAHL04TP-	Milligard RW06, 0.5 µm Filter Media Over Durapore Hydrophilic 0.45 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone
Durapore 0.22 µm Multimedia Cartridges 10”-30”	CV03--TP3,	Milligard RW03, 0.2 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone
Durapore 0.22 µm Multimedia Cartridges 10”-30”	CV06--TP3,	Milligard RW06, 0.5 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone

Table 1–1: Hydrophilic Durapore Cartridges—Materials of Construction, continued

Device	Item Number (abbreviated)*	Membrane**	Materials: Cage/ Core or Disk	Materials: Membrane Filter	Materials: Support Web	Materials: O-ring
Durapore 0.22 µm Multimedia Cartridges 10”-30”	CV19--TP3,	Milligard RW19, 1.2 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone
Durapore 0.22 µm Multimedia Cartridges 10”-30”	CVSC--TP3,	Milligard RW19, 1.2 µm and RW06, 0.5 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone
Durapore 0.22 µm Multimedia Cartridges 10”-30”	CVSS--TP3,	Milligard RW06, 0.5 µm and RW03, 0.2 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone
Durapore 0.22 µm Multimedia Cartridges 10”-30”	CVSX--TP3,	Milligard RW19, 1.2 µm and RW03, 0.2 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone
Millidisk®	MC-L----	Durapore Hydrophilic Membrane	Polysulfone	Modified PVDF	n/ a	Silicone

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Durapore Pore Sizes are as follows: GL 0.22 µm, HL 0.45 µm, VL 0.1 µm, and DR 0.65 µm. Milligard Media Nominal pore ratings are as follows: RW19 media 1.2 µm, RW06 media 0.5 µm, and RW03 media 0.2 µm.

Table 1–2: Hydrophilic Durapore Cartridges—Nominal Device Dimensions

Type	Item Number (abbreviated)*	Approx. Nominal Length (inch)	Approx. Nominal Length (cm)	Approx. Nominal OD** (inch)	Approx. Nominal OD (cm)
Millidisk 10	MC-L10---	1 7/ 8	4.8	n/ a	n/ a
Millidisk 20	MC-L20---	2 7/ 8	7.3	n/ a	n/ a
Millidisk 30	MC-L30---	3 7/ 8	9.9	n/ a	n/ a
Millidisk 40	MC-L40---	4 7/ 8	12.4	n/ a	n/ a
Durapore 5"	CV---5----	5"	12.7	2.7	6.9
Durapore 10"	CV---1---	10"	25.4	2.7	6.9
Durapore 20"	CV---2---	20"	50.8	2.7	6.9
Durapore 30"	CV---3---	30"	76.2	2.7	6.9
Optiseal Cartridges w/ Durapore Membrane	L--L04---	4"	10.2	2.3	5.7

* Refer to the Millipore Catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Outer diameter

Table 1–3: Hydrophilic Durapore Cartridges—Nominal Effective Filtration Area (EFA)

Type	Item Number (abbreviated)*	EFA (ft^2)	EFA (m^2)
Millidisk 10	MC-L10---	0.5	500 cm^2
Millidisk 20	MC-L20---	1.1	1000 cm^2
Millidisk 30	MC-L30---	1.6	1500 cm^2
Millidisk 40	MC-L40---	2.2	2000 cm^2
Durapore 5"	CV-L-5---	3.8	0.4 m^2
Durapore and Single Layer Milligard 10”	CV-L-1---, CV03-1TP3, CV06-1TP3, CV19-1TP3	7.4	0.7 m^2
Durapore and Single Layer Milligard 20”	CV-L-2---, CV03-2TP3 CV06-2TP3, CV19-2TP3	14.8	1.4 m^2
Durapore and Single Layer Milligard 30”	CV-L-3---, CV03-3TP3 CV06-3TP3, CV19-3TP3	22.2	2.1 m^2
Durapore and Double Layer Milligard 10”	CVSC-1TP3, CVSS-1TP3 CVSX-1TP3	6.0	0.6 m^2
Durapore and Double Layer Milligard 20”	CVSC-2TP3, CVSS-2TP3 CVSX-2TP3	12.0	1.2 m^2
Durapore and Double Layer Milligard 30”	CVSC-3TP3, CVSS-3TP3 CVSX-3TP3	18.0	1.8 m^2
Optiseal Cartridges w/ Durapore Membrane	L--L04---	1.9	0.2 m^2

Table 1–4: Hydrophilic Durapore Cartridges—Recommended Flush Volumes, Post Sterilization

Device	Item Number (abbreviated)*	Worst Case Pre-Test Treatment***	Recommended Flush Volume (mL)**
Charged Durapore Cartridges	CCGL-----	Autoclave at 126 °C for 30 minutes	1000 per 10"
Durapore 5" Cartridges	CV-L-5---	Autoclave at 126 °C for 60 minutes	500
Durapore Cartridges	CVDR--PP-, CVHL--PP-, CVGL-----, CVVL-----	Autoclave at 126 °C for 60 minutes	1000 per 10"
Durapore Multimedia Cartridges	CVDR--TP-, CVHL--TP-, CV19----, CV03----, CV06----, CVSC----, CVSS----, CVSX---	Autoclave at 121 °C for 60 minutes	1000 per 10"
Millidisk Cartridges	MC-L----	Autoclave at 126 °C for 60 minutes	200 per device
Optiseal Charged Durapore Cartridges	LCGL04---	Autoclave at 126 °C for 30 minutes	500
Optiseal Cartridges w/ Durapore Membrane	LAGL04---, LAVL04---	Autoclave at 126 °C for 30 minutes	500
Optiseal Multimedia Cartridges w/ Durapore Membrane	LAHL--TP-	Autoclave at 121 °C for 30 minutes	500

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Recommended flush volume to meet USP oxidizables test.

*** Pre-test treatment conditions described are not intended as a substitute for filter sterilization validation. Conducting an on-site filter sterilization validation study is the responsibility of the user.

Hydrophilic Durapore Capsules

This section lists the materials of construction, nominal device dimensions, nominal effective filter area, nominal hold up volume, and recommended flushes (post sterilization) of the hydrophilic Durapore capsule.

Table 1–5: Hydrophilic Durapore Capsules—Materials of Construction

Device	Item Number (abbreviated)*	Membrane**	Materials: Cage/ Core or Disk	Materials: Membrane Filter	Materials: Support Web	Materials: O-rings	Materials: Capsule Housing
Millipak® Capsules	MP-L----	Durapore Hydrophilic Membrane	Polycarbonate	Modified PVDF	n/ a	n/ a	Polycarbonate
Opticap™ 4" and 10" Capsules, Non-Sterile,	KPHL01---, KVGL01---, KVVL01---, KVGL04---, KVVL04---	Durapore Hydrophilic Membrane	Rigid Polypropylene	Modified PVDF	Spun-Bonded Polypropylene	Silicone O-rings in Vent Ports	Rigid Polypropylene
Opticap 4" and 10" Capsules, Non-Sterile, Gamma Compatible or Pre-Sterilized by Gamma	KVGLG1---, KVVLG1---, KVGLS1---, KVVLS1---	Durapore Hydrophilic Membrane	Gamma-Stable Rigid Polypropylene	Modified PVDF	Gamma Stable Spun-Bonded Polypropylene	Silicone O-rings in Vent Ports	Gamma Stable Rigid Polypropylene
Opticap 4" and 10" Capsules, Non-Sterile, Multimedia	KV03----	Milligard RW03, 0.2 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone O-rings in Vent Ports	Rigid Polypropylene
Opticap 4" and 10" Capsules, Non-Sterile, Multimedia	KV06----	Milligard RW06, 0.5 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone O-rings in Vent Ports	Rigid Polypropylene
Opticap 4" and 10" Capsules, Non-Sterile, Multimedia	KV19----	Milligard RW19, 1.2 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone O-rings in Vent Ports	Rigid Polypropylene
Opticap 4" and 10" Capsules, Non-Sterile, Multimedia	KVSC----	Milligard RW19, 1.2 µm and RW06, 0.5 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone O-rings in Vent Ports	Rigid Polypropylene
Opticap 4" and 10" Capsules, Non-Sterile, Multimedia	KVSS----	Milligard RW06 0.5 µm and RW03, 0.2 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone O-rings in Vent Ports	Rigid Polypropylene
Opticap 4" and 10" Capsules, Non-Sterile, Multimedia	KVSX----	Milligard RW19, 1.2 µm and RW03, 0.2 µm Filter Media Over Durapore Hydrophilic 0.22 µm Membrane	Rigid Polypropylene	Modified PVDF Membrane plus MEC on a polyester web	Spun-Bonded Polypropylene	Silicone O-rings in Vent Ports	Rigid Polypropylene

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Durapore Pore Sizes are as follows: GL 0.22 µm, HL 0.45 µm, VL 0.1 µm, and DR 0.65 µm. Milligard Media Nominal pore ratings are as follows: RW19 media 1.2 µm, RW06 media 0.5 µm, and RW03 media 0.2 µm.

Table 1–6: Hydrophilic Durapore Capsules—Nominal Device Dimensions

Type	Item Number (abbreviated)*	Configuration	Approx. Nominal Length** (inch)	Approx. Nominal Length** (cm)	Approx. Nominal OD*** (inch)	Approx. Nominal OD (cm)
Millipak 20	MP-L02-H-	1/4" (6 mm) step barb inlet and outlet	4	10	3	7.6
Millipak 20	MP-L02-F-	3/4" (19 mm) sanitary flange inlet and outlet	3.3	8.4	3	7.6
Millipak 40	MP-L04-K-	1/4" (6 mm) NPTM inlet and 1/4" (6 mm) step barb outlet	3.6	9.1	3	7.6
Millipak 40	MP-L04-H-	1/4" (6 mm) step barb inlet and outlet	4	10	3	7.6
Millipak 40	MP-L04-F-	3/4" (19 mm) sanitary flange inlet and outlet	3.5	8.9	3	7.6
Millipak 60	MP-L06CL-	1 1/2" (38 mm) sanitary flange Inlet, 1/4" (6 mm) step barb outlet	3.6	9.1	3	7.6
Millipak 60	MPSL06CB-	1/4" (6 mm) NPTM inlet and 1/4" (6 mm) step barb outlet	3.2	8.1	3	7.6
Millipak 60	MP-L06-H-	1/4" (6 mm) step barb inlet and outlet	4	10	3	7.6
Millipak 60	MP-L06-F-	3/4" (19 mm) sanitary flange inlet and outlet	3.7	9.4	3	7.6
Millipak 100	MP-L10CL-	1 1/2" (38 mm) sanitary flange inlet and outlet	5.1	13	3	7.6
Millipak 100	MP-L10CB-	1/4" (6 mm) NPTM inlet and outlet	2.9	7.4	3	7.6
Millipak 100	MP-L10CF-	3/4" (19 mm) sanitary flange inlet and outlet	4.2	11	3	7.6
Millipak 100	MP-L10CA-	9/16" (14 mm) barb inlet and outlet	3.3	8.4	3	7.6
Millipak 200	MP-L20CL-	1 1/2" (38 mm) sanitary flange inlet and outlet	6.1	15.5	3	7.6
Millipak 200	MP-L20CB-	1/4" (6 mm) NPTM inlet and outlet	3.9	10	3	7.6
Millipak 200	MP-L20CF-	3/4" (19 mm) sanitary flange inlet and outlet	5.2	13	3	7.6
Millipak 200	MP-L20CA-	9/16" (14 mm) barb inlet and outlet	4.3	11	3	7.6
Millipak 200	MP-L20CA-	9/16" (14 mm) barb inlet and outlet	4.3	11	3	7.6

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Measured from connection to connection.

*** Outer diameter

Table 1–6: Hydrophilic Durapore Capsules—Nominal Device Dimensions, continued

Type	Item Number (abbreviated)*	Configuration	Approx. Nominal Length** (inch)	Approx. Nominal Length** (cm)	Approx. Nominal OD*** (inch)	Approx. Nominal OD (cm)
Opticap 10"	KV-LG1TH1, KV-LS1TH1	1 1/2" (38 mm) sanitary flange inlet and 9/16" (14 mm) barb outlet	N/A	N/A	Body 3.3" End Cap 4.5"	Body 8.4 cm End Cap 11 cm
Opticap 10"	KV-LG1FH1, KV-LS1FH1	3/4" (19 mm) sanitary flange inlet and 9/16" (14 mm) barb outlet	N/A	N/A	Body 3.3" End Cap 4.5"	Body 8.4 cm End Cap 11 cm
Opticap 10"	KV-LG1TT1, KV-LS1TT1, KV-L01TC1, KP-L01TC1	1 1/2" (38 mm) sanitary flange inlet and outlet	13.7	35	Body 3.3" End Cap 4.5"	Body 8.4 cm End Cap 11 cm
Opticap 10"	KV-LG1FF1, KV-LS1FF1	3/4" (19 mm) sanitary flange inlet and outlet	13.7	35	Body 3.3" End Cap 4.5"	Body 8.4 cm End Cap 11 cm
Opticap 10"	KV-LG1HH1, KV-LS1HH1, KV-L01HB1, KP-L01HB1	9/16" (14 mm) barb inlet and outlet	13.3	34	Body 3.3" End Cap 4.5"	Body 8.4 cm End Cap 11 cm
Opticap 4"	KV-LG4TH3, KV-LS4TH3	1 1/2" (38 mm) sanitary flange inlet and 9/16" (14 mm) barb outlet	6.5	16.5	Body 2.4" End Cap 3.7"	Body 6.1 cm End Cap 9.4 cm
Opticap 4"	KV-LG4TT3, KV-LS4TT3, KV-L04TC3	1 1/2" (38 mm) sanitary flange inlet and outlet	6.7	17	Body 2.4" End Cap 3.7"	Body 6.1 cm End Cap 9.4 cm
Opticap 4"	KV-L04NP3	1/4" (6 mm) NPTM inlet and outlet	5.9	15	Body 2.4" End Cap 3.7"	Body 6.1 cm End Cap 9.4 cm
Opticap 4"	KV-L04FH3	3/4" (19 mm) sanitary flange inlet and 9/16" (14 mm) barb outlet	6.5	16.5	Body 2.4" End Cap 3.7"	Body 6.1 cm End Cap 9.4 cm
Opticap 4"	KV-L04FF3	3/4" (19 mm) sanitary flange inlet and outlet	6.7	17	Body 2.4" End Cap 3.7"	Body 6.1 cm End Cap 9.4 cm
Opticap 4"	KV-LG4HH3, KV-LS4HH3, KV--04HB3	9/16" (14 mm) barb inlet and outlet	6.3	16	Body 2.4" End Cap 3.7"	Body 6.1 cm End Cap 9.4 cm

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Measured from connection to connection.

*** Outer diameter

Table 1–7: Hydrophilic Durapore Capsules—Nominal Effective Filtration Area (EFA)

Device	Item Number (abbreviated)*	EFA (ft^2)	EFA (m^2)
Millipak 20	MP-L02---	0.1	100 cm^2
Millipak 40	MP-L04---	0.2	200 cm^2
Millipak 60	MP-L06----	0.3	300 cm^2
Millipak 100	MP-L1-----	0.5	500 cm^2
Millipak 200	MP-L2----	1.1	0.1 m^2
Opticap 10" Capsules, Non-Sterile	KPHL01---, KVGL01---, KVVL01---	7.4	0.7 m^2
Opticap 10" Capsules, Non-Sterile, Gamma Compatible or Pre-Sterilized by Gamma	KV-LG1---, KV-LS1---	7.8	0.7 m^2
Opticap 4" Capsules, Non-Sterile	KV-L04---	1.5	0.14 m^2
Opticap 4" Capsules, Non-Sterile, Gamma Compatible or Pre-Sterilized by Gamma	KV-LG4---, KV-LS4---	1.6	0.15 m^2
Opticap 4" Multimedia Capsules, Non-Sterile	KV0304---, KV0604---, KV1904---	1.5	0.14 m^2
Opticap 4" Multimedia Capsules, Non-Sterile	KVSC04---, KVSS04---, KVSX04---	1.2	0.11m^2

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

Table 1–8: Nominal Hold Up Volume

Product Designation	Item Number (abbreviated)*	Upstream Volume (nominal)	Hold Up Volume Exceeding Bubble Point
Millipak 20	MPGL02---	30 mL	1 mL
Millipak 40	MPGL04---	40 mL	2 mL
Millipak 60	MPGL06---	50 mL	2 mL
Millipak 100	MPGL10---	70 mL	3 mL
Millipak 200	MPGL20---	110 mL	7 mL
Durapore 10” Cartridge	CVGL-----	3000 mL	90 mL
4” Opticap	KVGL04---	140 mL	20 mL
10” Opticap	KVGL01---	640 mL	90 mL

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

Table 1–9: Hydrophilic Durapore Capsules—Recommended Flush Volumes (Post Sterilization)

Device	Item Number (abbreviated)*	Worst Case Pre-Test Treatment**	Recommended Flush Volume (mL)***
Millipak, Non-Sterile Capsules	MP-L0----, MP-L1----, MP-L2----	Autoclave at 123 °C for 90 min	200
Millipak, Pre-Sterilized by Gamma Capsules	MP-L-G---, MP-L--G--	Irradiation	200
Opticap 10" Capsules, Non-Sterile	KPHL01---, KVGL01---, KVVL01---	Autoclave at 126 °C for 60 min	1000
Opticap 10" Capsules, Non-Sterile, Gamma Compatible	KVGLG1---, KVVLG1---	N/A	1000
Opticap 10" Capsules, Pre-Sterilized by Gamma	KVGLS4---, KVVLS4---	Irradiation	500
Opticap 4" Capsules, Non-Sterile	KVG04---	Autoclave at 126 °C for 30 min	500
Opticap 4" Capsules, Non-Sterile, Gamma Compatible	KVGLG4---, KVVLG4---	N/A	1000
Opticap 4" Capsules, Pre-Sterilized by Gamma	KVGLS1---, KVVLS1---	Irradiation	1000
Opticap 4" Multimedia Capsules, Non-Sterile	KV0304---, KV0604---, KV1904---, KVSC04---, KVSS04---, KVSX04---	Autoclave at 123 °C for 30 min	1000
Opticap 4" Multimedia Capsules, Non-Sterile 0.45 µm	KVHL01---	Autoclave at 121 °C for 60 min	1000

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Pre-test treatment conditions described in this table are not intended as a substitute for filter sterilization validation. The user is responsible for conducting an on-site filter sterilization validation study.

*** Recommended flush volume to meet the USP Oxidizables Test.

Additional Literature on Hydrophilic Durapore Cartridges and Capsules

Contact Millipore to obtain the following literature for more details on available catalogue numbers:

- Millipore Pharmaceutical Process Separations Catalogue
- Product Data Sheets
- Product Application Notes
- Millipore Validation Guides
- Millipore Validation Services

Or visit our web site at www.millipore.com

Chapter 2

Installation of Hydrophilic Durapore Cartridges and Capsules

Introduction

This chapter provides information on:

- Filter inspection
- Filter box contents
- Guidelines for filter installation, including suggestions for the proper handling of cartridges and capsules
- Filter shelf life and storage conditions

Inspecting the Filter

When you receive a new box of filters, visually inspect them to ensure that they were not damaged during shipping. The outer box should be intact and in good condition. The outer bags within the box that protect the filters should also be intact. If necessary, call Millipore Technical Service to report any damage. In the U.S., call **1-800-MILLIPORE** (1-800-645-5476). Outside the U.S., see your Millipore catalogue for the phone number of the Millipore office nearest you. Or contact Millipore Technical Service by e-mail at tech_service@millipore.com.

Unpacking the Box

Your box of Durapore filters should include:

- **Certificate of Quality**

  The Certificate of Quality provides detailed product properties and performance data. It is product specific and typically lists lot release criteria, product audit criteria, and in-process testing.

- **Wetting Instructions**

  The Wetting Instructions provide helpful procedural information on how to completely wet the filter to ensure optimum performance.

- **Change Notification**

  If a minor change is made to the product or packaging, you may find a change notification statement in the box in accordance with Millipore's Change Notification policy.

Installing the Filter

Before using the filter, verify the pore size and the catalogue number.

Pore Size Verification—Cartridges

For cartridges, the catalog number, lot number and pore size are located on top of the cartridge as shown. The appearance of the cartridge is the same regardless of pore size.

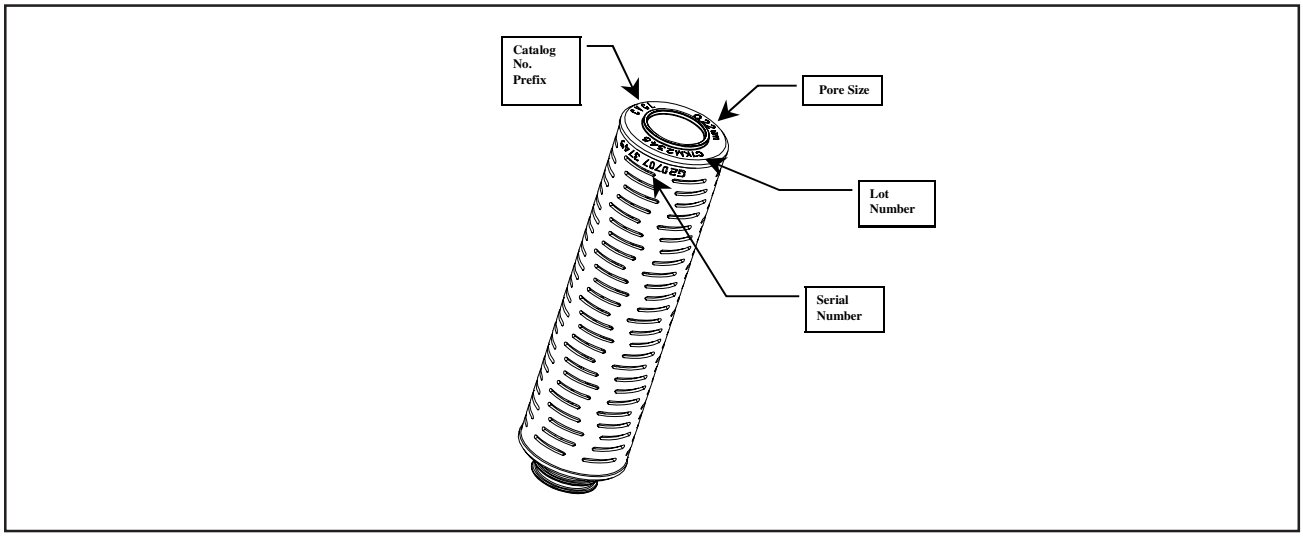


Figure 2–1: Durapore cartridge filter catalog number, pore size, and lot number location

Usage Guidelines for Cartridges

It is very important that you install the filter in the housing correctly. The cartridges are shipped double-bagged. Carefully tear open the outer bag, then carefully tear open the inner bag. Use the inner bag as a glove to avoid touching the cartridge with ungloved hands as you install it into the housing. To ease installation of the cartridge into the housing, wet the O-rings with sterile water and gently slide the cartridge into place. For a Code 7 cartridge, after the O-rings are in the socket, twist the cartridge slightly to "lock" it in place. When installing the cartridge, avoid pinching the O-rings or bending the tabs on the Code 7 cartridge. A pre-use integrity test can confirm that you installed the filter in the housing correctly. (See Chapter 4 for details on filter integrity testing.)

NOTE: Do not touch a cartridge with ungloved hands since dirt and oils from your skin can affect the performance of the filter.

Pore Size Verification—Capsules

Millipak™ and Opticap™ filters have color-coded labels that list the catalogue number, lot number and pore size. The Millipak label is located at the top of the inlet side of the filter. The Opticap label is located along the length of the Opticap housing.

Table 2–1: Color Code for Hydrophilic Durapore Capsule Filter Pore Size

Color	Pore Size
Orange	0.1 µm
Yellow	0.22 µm
Red	0.45 µm

Usage Guidelines for Millipak/ Opticap Capsule Filters

- Avoid dropping these filters. If a Millipak or Opticap filter accidentally drops on the floor, perform a pre-use integrity test to ensure that the filter was not damaged. (See Section 4 on filter integrity testing.)
- Use sterile technique. Certain Millipak and Opticap filters are shipped in a pre-sterile configuration. To prevent accidentally contaminating the filter, handle the outside of the housing only. Do not touch any of the inlet or outlet fittings of a capsule with ungloved hands.
- Orient Millipak and Opticap filters vertically. The inlet can be at the top or bottom. For Millipak and Opticap filters, it is strongly recommended that flow be in the forward direction (inlet to outlet) because the filter is structurally stronger in the forward flow direction.

  NOTE: Millipak filters: The inlet side of the housing is clear; the outlet side is opaque.
  Opticap filters: An arrow indicates direction of flow.

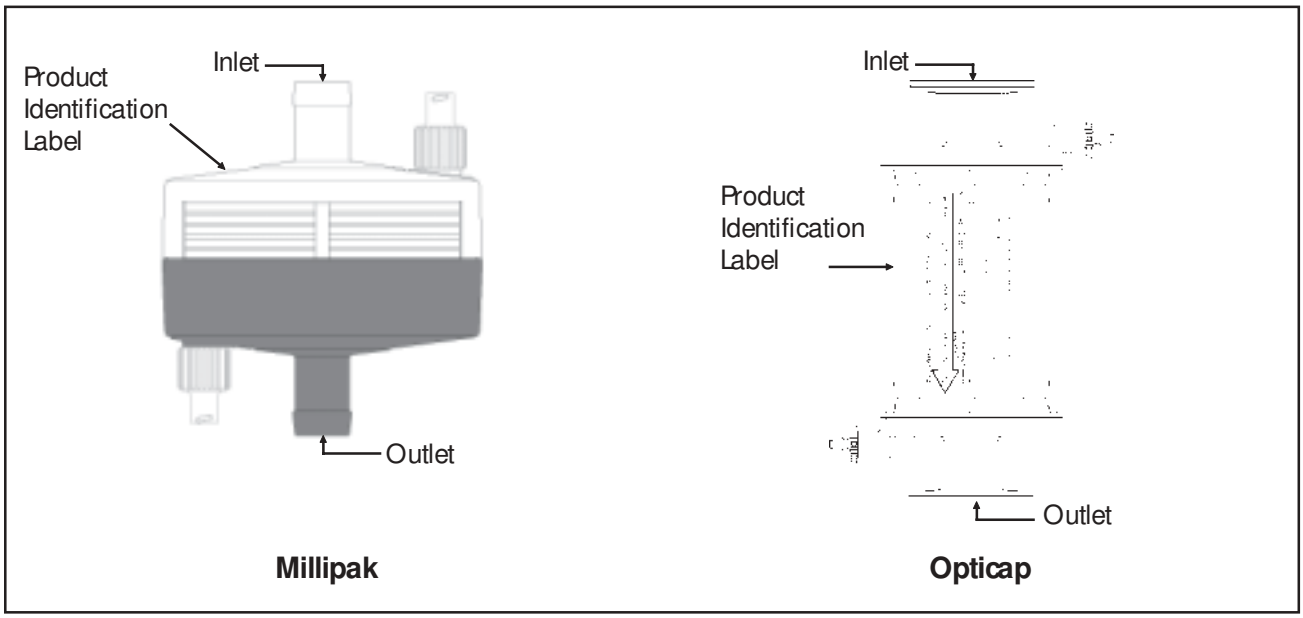


Figure 2–2: Capsule filter catalogue number, pore size and lot number location

- For Millipak/Opticap Filters with Hosebarb Connections:
  Use tubing clamps to secure the tubing to the hosebarb connections; this prevents the tubing from slipping off the hosebarb accidentally when under pressure.
- For Millipak/Opticap Filters with Sanitary Flanges:
  Do not overtighten the sanitary flange. "Finger tight" is sufficient. Overtightening can result in cracking the fitting. Use caution when connecting a plastic Millipak/Opticap fitting to a stainless steel fitting.

Storing the Filter

Millipore assigns an expiration date only to sterile Millipak and Opticap filters (two years from the date of manufacturing for Millipak filters, three years from the date of manufacturing for Opticap filters). Millipore recommends that you store filters in their original packaging, away from direct sunlight, and at room temperature. We also recommend that you integrity test all Durapore filters before use to ensure there was no damage during shipping or storage. (See Chapter 4 on filter integrity testing.)

Chapter 3

Steam Sterilization of Hydrophilic Durapore Cartridges and Capsules

Introduction

This chapter describes how to properly steam sterilize hydrophilic Durapore cartridges and capsules, including:

- Background information on steam sterilization
- General guidelines and Standard Operating Procedures (SOPs) for Steam In Place (SIP)
- General guidelines and Standard Operating Procedures (SOPs) for autoclaving

CAUTION: Read this chapter carefully since improper steam sterilization can often damaged filters.

Overview of Steam Sterilization

The simplest definition of sterility is the complete absence of life as seen through growth or reproduction. Something can be proven sterile by conducting tests to show that nothing grows in or on it. Drug manufacturers go to great lengths to validate the sterility of their parenteral products. Sterility of parenteral products is critical because the presence of viable microorganisms or their by-products (endotoxins) is detrimental.

The most common sterilization method is steam under pressure. This method of sterilization is done, in situ (Steam In Place) or in an autoclave. In either case, moist heat (water-saturated steam under pressure) is used. The moist, hot environment is an effective method of sterilization because the moist heat irreversibly denatures vital enzymes that result in the death of microorganisms. Moisture contributes a great deal to the process. Saturated steam at 121 °C supplies seven times more available heat than air at the same temperature. Saturated steam has a unique temperature at each pressure (for example, 15 psig at 121 °C). See Table 3-1 for details.

Table 3–1: Saturated Steam Pressure and Temperature

Saturated Steam Pressure (psig)	Saturated Steam Temperature (°C)
15	121
21	126
31	135
46	145

Steam sterilization is the most studied method of sterilization and is predictable and reproducible under defined operating conditions. Steam sterilization processes are characterized by measuring their microorganism kill efficiency. *Bacillus stearothermophilus* spores are used as the challenge organism because they are particularly resistant to moist heat and represent the worst case scenario.

This section describes how to sterilize Millipore cartridges and capsules without damaging the filters and compromising filter integrity. The steaming and autoclave cycle conditions mentioned in the SOPs and the guidelines are based on the thermal and hydraulic stress resistance of the filters. These recommendations are not intended as a substitute for filter sterilization validation. You must still perform on-site validation tests.

Steam Requirements

Whether you use Steam in Place (SIP) or autoclaving, you should supply pure steam. Pure steam is uncondensed WFI (Water For Injection). It is free of pyrogens, chemicals, particles and microorganisms, and must be supplied dry, saturated, and free of non-condensable gases and condensate.

Table 3–2: Recommended Feed Water Quality for Pure Steam

Conductivity	Silica	Amine	Chlorine	Bacterial Endotoxins*
not to exceed 5 microsiemens (µS)/ cm	not to exceed 1 ppm**	below 100 ppm	below 100 ppm	not more than 0.25 EU/ mL

* EU = Endotoxin Units

** PPM = Parts Per Million

Steaming In Place of Hydrophilic Durapore Cartridges

Steaming In Place (SIP) has the following advantage and disadvantage:

- **SIP advantage:**
  Reduces the number of manipulations and aseptic connections that might compromise the sterility of the downstream equipment

- **SIP disadvantage:**
  Uses flowing steam; accidental differential pressure at high temperature that can damage a cartridge

▲ **WARNING: Do not, under any circumstances, SIP capsule filters; see the "Autoclaving Hydrophilic Durapore" section in this chapter for details.**

Table 3–3 lists the maximum SIP conditions for Durapore cartridges and the number of SIP cycles that the cartridges can withstand.

Table 3–3: Hydrophilic Durapore Cartridges — Maximum Sterilization Cycles (SIP)

Device	Item Number (abbreviated)	In-Line Steam
Charged Durapore Cartridges	CCGL-----	135 °C, 30 minutes, 10 times, max*
Durapore 5" Cartridges	CV-L-5---	135 °C, 30 minutes, 30 times, max*
Durapore Cartridges	CVDR--PP-, CVHL--PP-, CVGL-----, CVVL-----	135 °C, 30 minutes, 30 times, max*
Durapore 0.45 µm and 0.65 µm Multimedia Cartridges	CVDR--TP-, CVHL--TP-	121 °C, 30 minutes, 10 times, max*
Durapore 0.22 µm Multimedia Cartridges	CV03--TP3, CVSC--TP3, CV06--TP3, CVSS--TP3, CV19--TP3, CVSX--TP3	123 °C, 30 minutes, 6 times, max*
Millidisk Cartridges	MC-L-----	135 °C, 60 minutes, 5 times, max*
Optiseal Charged Durapore Cartridges	LCGL04--	135 °C, 30 minutes, 10 times, max*
Optiseal Cartridges w/ Durapore Membrane	LAGL04---, LAVL04---, LAHL04PP-	135 °C, 30 minutes, 30 times, max*
Optiseal Multimedia Cartridges w/ Durapore Membrane	LAHL04TP	121 °C, 30 minutes, 10 times, max*

* These are the maximum conditions Durapore cartridges have been validated to withstand. Select the time and temperature appropriate to validate the proper sterilization of the device and housing. The recommendations in this table are not intended as a substitute for filter sterilization validation. The user is responsible for on-site filter sterilization validation studies.

SIP System Design Overview

Figure 3–1 is a schematic of the filter assembly or target unit to steam in place. This schematic includes the filter, the filter housing, valves, pressure and/or temperature gauges.

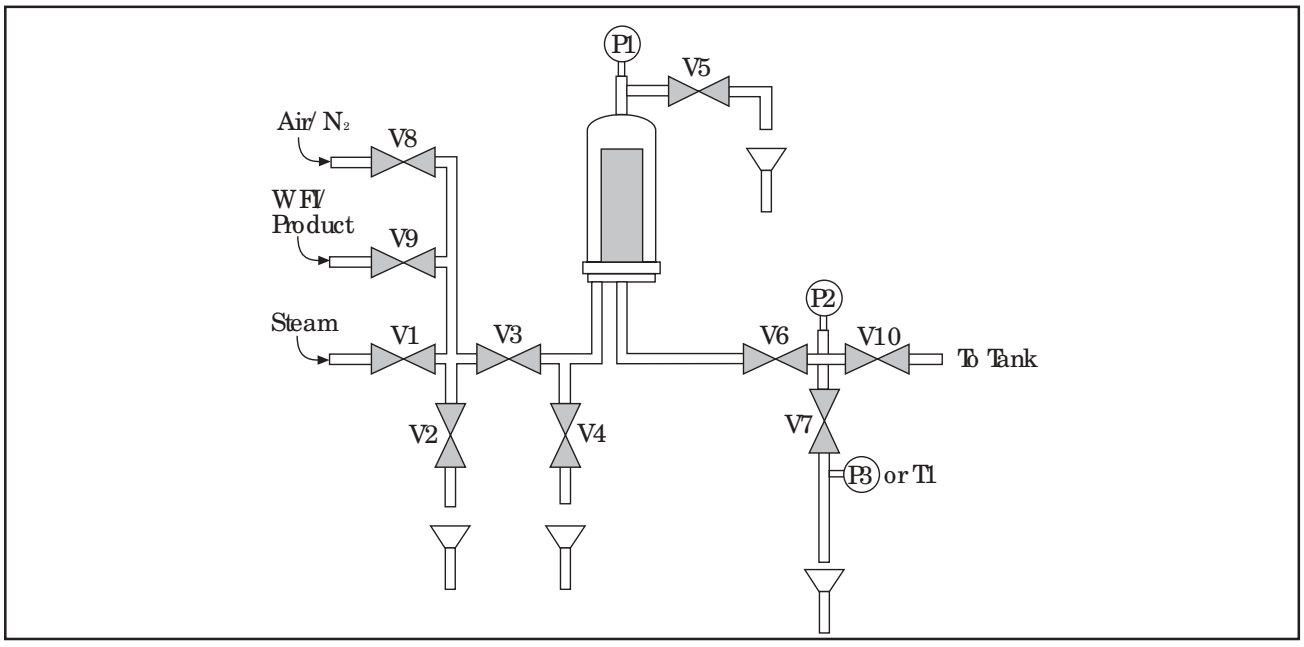


Figure 3–1: Typical sterile filter cartridge and housing assembly for SIP

SIP System Design Considerations

Consider the following when designing an SIP system:

- **Air Removal**
  The ideal air removal system allows steam to enter at the high points and air to flush out at the low points of the system. This setup is ideal because air (molecular weight 29 g/mol) is heavier than steam (molecular weight 18 g/mol) and naturally tends to sink to the low points. But, this setup is not always practical. Fortunately, the steam flow rates used are sufficient to force all the air out of the system even when steam enters at a low point. Minimize dead legs (section of pipe where the length is six times the diameter). If a dead leg exists, install an air vent to prevent air from being trapped in this part of the system during steaming.

- **Condensate Removal**
  Install drain valves or steam traps every 100 ft of steam piping, upstream of control valves and normally closed isolation valves, on the upstream side of the filter housing, and at the bottom of any vertical risers. Angle horizontal sections of pipe downward to prevent condensate collection (1:120 or 1 inch every 10 ft). Use air breaks on the condensate drains to prevent siphoning of condensate during system cooling.

- **Temperature Gauge Placement**
  Position a monitoring temperature gauge at the slowest heating or coldest spot in the system, generally the farthest drain point from the steam source. During validation, the coldest spots in the system are determined by means of thorough coverage of the system with thermocouples.

SIP Standard Operating Procedure

The procedure for performing SIP consists of the following stages:

1. Post integrity test blow down (only necessary if you performed an integrity test or filter flushing before steaming)
2. Steaming
3. Post steaming blow down

Precautions

Before starting the procedure, check the following:

- The proper filter (pore size, catalogue number) has been selected and the filter is installed in the housing correctly. (See Chapter 2 for proper filter installation.)
- All valves are closed and tubing is attached to bleed valves and directed to condensate drain.
- People participating in the steaming process are appropriately trained and wearing protective glasses and heat resistant gloves.

▲ **WARNINGS: Avoid unprotected contact with steam or hot stainless steel surfaces to prevent bodily injury. And do not, under any circumstances, SIP capsule filters; see the "Autoclaving Hydrophilic Durapore" section in this chapter for details.**

If you did not perform a pre-sterilization integrity test or flush the filter and the filter is dry, skip the following section. Instead, see "Filter Steaming" in this chapter.

Post Integrity Test Blow Down

Millipore recommends performing an integrity test pre- and post-filtration. (See Chapter 4 for details on filter integrity testing.) If you decide to integrity test or flush prior to steam sterilization, the membrane in the cartridge will be wet. Blowing down the cartridge with clean air or nitrogen to remove water from the pores eliminates the possibility of exceeding the maximum differential pressure specification of 5 psid when steaming. If you choose not to perform a pre-sterilization integrity test, the filter will be dry out of the box. Skip this section and see "Filter Steaming" in this chapter.

1. Clear a path for the compressed gas flow through the filter to drain. (Open V3, V6, and V7.) Refer to Figure 3–1.
2. Set compressed gas pressure to 5 psi. Start compressed gas flow into the filter. (Open V8.) Slowly increase pressure to 10 psi above the bubble point of the installed membrane cartridge
3. Allow gas to flow for 5 minutes (to force all water out of the pores and dry the filter).
   NOTE: As the filter dries, the air flow rate will increase and the differential pressure decreases.
4. Shut off the gas supply and close all valves (V8, V3, V6, and V7) after 5 minutes.

Filter Steaming

Perform this procedure on a dry filter to prevent damaging it and compromising its integrity.

1. Check that steam supply and compressed gas pressures are set up at the values determined during the validation process for steam sterilization of the specific system being used.
2. Purge the steam line until all condensate is gone. (Open V1 and V2.)
3. Allow for subsequent air and condensate removal. (Fully open V4 and V5.)

   NOTE: Trapped air or condensate acts as a barrier to heat transfer and inhibits effective steam penetration. These conditions can lead to less moist heat contact and lower sterilization temperatures of the target unit. Condensate resistance to heat transfer is 70 times greater than that of stainless steel. Air resistance to heat transfer is 25 times greater than that of water. Accumulated condensate can be accelerated by flowing steam, producing what is known as a water hammer. Removing condensation prevents a water hammer from forming and damaging the filter.
4. Introduce steam progressively and heat up the filter. (Slowly open V3.)
5. Partially close bleed valves (V2, V4, and V5) so that you can see a 6-inch wisp of steam and a continuous drip of condensate exiting.
6. Establish a steady flow of steam and allow for condensate drainage and air removal from the filter housing. (Fully open V6, then crack open V7.)

   NOTE: Control the pressure drop across the filter (P1-P2). The differential pressure across the filter (P1-P2) should not exceed 5 psid. Only a small flow of steam is required to heat up the assembly because steam can effectively transfer a large amount of heat (approximately 1000 BTU/lb).
7. Ensure that all air and condensate are effectively removed. (Keep V2, V4, V5, and V7 cracked open so that you can see a 6-inch wisp of steam and a continuous drip of water exiting.)
8. Start timing the sterilization cycle when the pressure gauge (P3) reaches the validated pressure or the temperature gauge (T1) reaches the validated temperature. Record both temperature and pressure regularly during the sterilization phase.
9. Close the steam supply valve and introduce sterile compressed gas into the system when the sterilization process completes. (Close V1 and slowly open V8.)

   NOTE: Make sure that the system remains under positive pressure (as indicated by P1 and P2). The differential pressure (P1-P2) should not exceed 5 psid.

Post Steaming Blow Down

This procedure ensures positive pressure and accelerated system cooling.

1. Allow for steam purge from all valves. (Close V2 and V4 to increase the flow of gas through the system.) Maintain the flow to cool down the system until the temperature gauge T1 indicates approximately 30 °C.
2. Respectively close valves (V7, V6 and V4 and V5). Keep the compressed gas flow on and the filter inlet open to maintain a positive pressure into the sterile filter system while not in use.

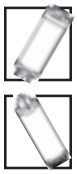
The system is now ready for integrity testing. See Chapter 4 for information on integrity testing.

Troubleshooting the SIP Procedure

If filter damage occurs, check Table 3–4 to troubleshoot the probable cause of the damage. The table lists probable causes and solutions for some of the problems you may encounter during the SIP procedure.

Table 3–4: Cartridge Filter Failure Modes from SIP

Description of Failure	Cause	Action to Prevent
Core collapse	Exceeded specification forward hydraulic stress at SIP temp	Reduce differential pressure at SIP temp
Code 7 tabs bent down	Exceeded specification reverse hydraulic stress at SIP temp	Reduce differential pressure at SIP temp
Cartridge meltdown	Exceeded polypropylene melting point of 168 °C	Check steam temp & pressure
Sleeve warping	Exceeded specification SIP temperature	Check steam temp & pressure
Hydrolysis	Exceeded specifications for SIP cycles for polymers	Replace cartridge at recommended intervals
Oxidation	Exceeded specifications for exposure limits for time/ temp in air	Replace cartridge at recommended intervals
Sleeve ballooning	Exceeded specification reverse stress at SIP temp	Reduce differential pressure at SIP temp
Brown or green color	Contaminants in steam	Check pH of steam & or add pre-filtration
O-ring distortion	Exceeded specification SIP temp	Check steaming conditions & replace O-rings



Autoclaving Hydrophilic Durapore Capsules and Cartridge/ Housing Assemblies

Autoclaving capsules and cartridge/housing assemblies has an advantage and disadvantage:

- **Autoclaving advantage:**
  Uses passive steam that does not create damaging differential pressure during the process.

- **Autoclaving disadvantage:**
  Once the filter is removed from the autoclave, it must be installed aseptically before use.

▲ **WARNING: Do not, under any circumstances, SIP capsule filters.**

See Tables 3–5 and 3–6 for the maximum conditions for autoclaving Durapore filters and the number of autoclave cycles that the cartridges can withstand.

Table 3–5: Hydrophilic Durapore Cartridges — Maximum Sterilization Cycles (Autoclaving)

Device	Item Number (abbreviated)	Autoclave
Charged Durapore Cartridges	CCGL-----	126 °C, 30 minutes, 10 times max*
Durapore 5" Cartridges	CV-L-5---	126 °C, 60 minutes, 30 times max*
Durapore Cartridges	CVDR--PP-, CVHL--PP-, CVGL-----, CVVL-----	126 °C, 60 minutes, 30 times max*
Durapore 0.45 µm and 0.65 µm Multimedia Cartridges	CVDR--TP-, CVHL--TP-	121 °C, 60 minutes, 10 times max*
Durapore Cartridges 0.22 µm Multimedia Cartridges	CV03--TP3, CVSC--TP3, CV06--TP3, CVSS--TP3 CV19--TP3, CVSX--TP3	123 °C, 30 minutes, 6 times max*
Millidisk Cartridges	MC-L-----	126 °C, 60 minutes, 5 times max*
Optiseal Charged Durapore Cartridges	LCGL04---	126 °C, 30 minutes, 10 times max*
Optiseal Cartridges w/ Durapore membrane	LAGL04---, LAVL04---, LAHL04PP---	126 °C, 30 minutes, 10 times max*
Optiseal Multimedia Cartridges w/ Durapore membrane	LAHL04TP-	12 °C, 30 minutes, 10 times max*

* These are the maximum conditions Durapore cartridges have been validated to withstand. Select the time and temperature appropriate to validate the proper sterilization of the device and housing. The recommendations in this table are not intended as a substitute for filter sterilization validation. The user is responsible for an on-site filter sterilization validation study.

Table 3–6: Hydrophilic Durapore Capsules — Maximum Sterilization Cycles (Autoclaving)

Device	Item Number (abbreviated)	In-Line Steam	Autoclave
Millipak Capsules			
Non-Sterile	MP-L0----, MP-L1----, MP-L2----	Not Recommended	123 °C, 90 minutes, 3 times, max*
Pre-Sterilized by Gamma	MP-L-G---	Not Recommended	123 °C, 90 minutes, 3 times, max*
Opticap 10" Capsules			
Non-Sterile	KPHL01---, KVGL01---, KVVL01---	Not Recommended	126 °C, 60 minutes, 3 times, max*
Non-Sterile, Gamma Compatible	KVGLG1---, KVVLG1---	Not Recommended	Capable of 45 kilogram gamma, single dose, or 123 °C, 60 minutes, 3 times, max*
Pre-Sterilized by Gamma	KVGLS4---, KVVLS4---	Not Recommended	123 °C, 60 minutes, 3 times, max*
Opticap 4" Capsules			
Non-Sterile	KVG-04---	Not Recommended	126 °C, 60 minutes, 3 times, max*
Non-Sterile, Gamma Compatible	KVGLG4---, KVVLG4---	Not Recommended	Capable of 45 kilogray gamma, single dose, or 123 °C, 60 minutes, 3 times, max*
Pre-Sterilized by Gamma	KVGLS1---, KVVLS1---	Not Recommended	123 °C, 60 minutes, 3 times, max*
Opticap 4" Multimedia Capsules			
Non-Sterile	KV0304---, KV0604---, KV1904---, KVSC04---, KVSS04---, KVSX04---	Not Recommended	123 °C, 60 minutes, 3 times, max*
Non-Sterile 0.45 µm	KVHL01---	Not Recommended	121 °C, 60 minutes, 10 times, max*

* These are the maximum conditions Durapore capsules have been validated to withstand. Select the time and temperature appropriate to validate the proper sterilization of the device.

Autoclave Standard Operating Procedure

The procedure for autoclaving Durapore filters consists of two stages:

1. Filter preparation (pre-autoclave loading)
2. Autoclave loading

Filter Preparation

This section includes guidelines for vent positions, inlet and outlet openings, tubing, and clamp and fitting attachments.

Millipore recommends performing an integrity test pre- and post-filtration. (See Chapter 4 for details on filter integrity testing.) If you decide to perform a pre-sterilization integrity test, the membrane in the capsule will be wet. Unlike Steam In Place, however, you can autoclave filters wet or dry, as long as they are autoclaved using the same conditions used for filter sterilization validation.

1. Open filter vents and make sure that they remain open throughout the entire sterilization cycle. (The vents provide proper air displacement and condensate removal only when open and unobstructed.)

   NOTE: Trapped air or condensate acts as a barrier to heat transfer and inhibits effective steam penetration. These conditions can lead to less moist heat contact and lower sterilization temperatures of the target unit. Condensate resistance to heat transfer is 70 times greater than that of stainless steel. Air resistance to heat transfer is 25 times greater than that of water.

2. Ensure that the filter inlet and outlet openings are open and unobstructed to allow maximum air displacement and steam flow.
3. Ensure that any tubing attached to the filter is open and unobstructed to provide for adequate steam flow.

   NOTE: The tubing should be of the largest possible inner diameter, should not exceed 4 feet in length, should not be crimped, bent or U-shaped. If tubing is present on both inlet and outlet, it should not be connected in a continuous loop.

Filter Preparation, continued

4. Ensure that all open vents, open inlets, and open outlets are covered with suitable barrier paper. Alternatively, place the filter in an autoclave bag.
5. **If using sanitary clamps with capsule filters, do not overtighten the clamps. Overtightening can distort the fittings.** Use three-piece sanitary clamps, if necessary.

   NOTE: Three-piece sanitary clamps are preferred over two-piece clamps since they provide more uniform stress distribution.
6. If you attached stainless steel parts, do not allow capsule fittings to support the weight of these attachments. Use separate support structures to eliminate stress on the capsule fittings.

   NOTE: The weight of unsupported attachments coupled with the loss of the fitting's rigidity at the autoclave temperatures can deform and damage the capsule.

Autoclave Loading

Place the filter into the autoclave as follows:

The ideal filter orientation is in the upright or normal operating position (direction of flow) with the core (outlet) facing downward. If the filters are oriented horizontally or upside down, condensate accumulates in the core. The filter can be autoclaved while attached to the piece of process equipment. Or, place the filter in a basket or loose in the autoclave chamber.

NOTE: Ensure that the openings are covered with suitable barrier paper or place the entire filter in an autoclave bag.

Troubleshooting the Autoclaving Procedure

If filter damage occurs, check Table 3–7 to troubleshoot the probable cause of the filter damage. The table lists probable causes and possible solutions for some of the problems you may encounter during autoclaving.

Table 3–7: Cartridge Filter Failure Modes from Autoclaving

Description of Failure	Cause	Action to Prevent
Loss of capsule roundness	Capping off of inlet and outlet connections or, joining the inlet and outlet tubing or, crimping any inlet or outlet tubing	Ensure inlet & outlet connections are open and unobstructed. Do not join inlet and outlet connections. Ensure that inlet & outlet tubing is not crimped.
Distortion of fittings	Supporting excessive weight	Do not use connections to support excessive weight.
Distortion of vents	Vents used to support weight of capsule during autoclaving	Do not use filter vents to support the weight of the capsule.

Additional Steam Sterilization Literature

Contact Millipore to obtain the following literature for more details on Steam Sterilization.

- Technical Brief (Principles of Moist Heat Sterilization) Lit. No. ET010EN00 Rev. -09/00
- Reprint from Genetic Engineering News (Cartridge Filter Steaming-in-Place Allows Single-Unit Downstream Sterilization) September 1, 1997
- Technical Brief (General Principles of Steam-In-Place) Lit. No. TB059 Copyright 4/91
- Technical Brief (Principals of Steam-In-Place) Lit. No. ET011EN00 Rev. A-08/00
- Technical Brief (Millipore Steam Sterilization & Integrity Testing Procedures) Lit. No. ET015EN00 Rev. -09/00
- Technical Brief (Opticap Disposable Capsule Filters Autoclave Guidelines) Lit No. TB072

Chapter 4

Pre-Use Integrity Testing of Hydrophilic Durapore Cartridges and Capsules

Introduction

This chapter describes how to properly integrity test hydrophilic Durapore cartridges and capsules. Integrity tests provide assurance that a sterile filter will perform as intended prior to performing the entire filtration process. This chapter includes:

- Background on integrity testing
- General guidelines and Standard Operating Procedures (SOP) for membrane wetting
- General guidelines and Standard Operating Procedures for bubble point integrity testing
- General guidelines and Standard Operating Procedures for diffusion integrity testing
- Comparison of using bubble point integrity test versus diffusion integrity test

Overview of Integrity Testing

The integrity test of sterilizing grade filters is a generally accepted requirement in critical process filtration applications, particularly in the pharmaceutical industry. FDA regulations of large volume parentals (LVP) and small volume parentals (SVP) place an obligation on the user to test the integrity of these filters. Section 7.5 of the PDA Technical Report No 26 states that: "It is generally regarded as a cGMP requirement that filter or filter systems routinely be integrity tested both prior to and after use."

The FDA also requires corresponding documentation on integrity testing to be included with batch product records. There are also sound economic reasons for integrity testing sterilizing filters before use and after the batch has been filtered. The ability to monitor filter integrity before use prevents batch processing with a non-integral filter. A post-use integrity test verifies that the filter performed as specified. This allows rapid reprocessing and avoids waiting for the results of product sterility testing. Therefore, it is important that the user understand the principles and procedures of non-destructive integrity testing.

There are two categories of integrity testing: the destructive and non-destructive methods. Destructive integrity test methods leave the tested filter unfit for further use. Non-destructive integrity test methods allow the continued use of the filter after testing. The bacterial challenge test is an example of a destructive test. Non-destructive methods include bubble point and diffusion. You can perform non-destructive integrity tests manually or by using an automatic integrity tester. This guide focuses on manual methods. However, many users use automatic testers. You can apply the concepts described in this guide to either method. For more information on operating automatic integrity testers, refer to the user manual that came with your automatic integrity tester instrument.

Destructive Testing

The principle of bacterial challenge testing is to subject a sterilizing membrane to bacteria under the most severe conditions that the membrane would encounter during actual use. In essence, the challenge test consists of exposing the membrane to bacteria, subjecting it to stringent pressure and flow conditions, and analyzing the effluent for the presence or absence of the challenge organism.

The standard organism for challenge testing, *Brevundimonas diminuta* ATCC 19146 is chosen for its small size and its viability in the aqueous stream. In the challenge test, 10^7 colony forming units (CFU) per cm^2 of filtration surface area are used.

Challenge testing is designed to provide the membrane manufacturer with the assurance that the membrane, and fabricated device, meet the critical performance criteria of a sterilizing-grade filter. The test is performed by the filter manufacturer on a statistical sample of each lot of filters produced. However, this test is a “destructive test” because you cannot reuse the tested filters.

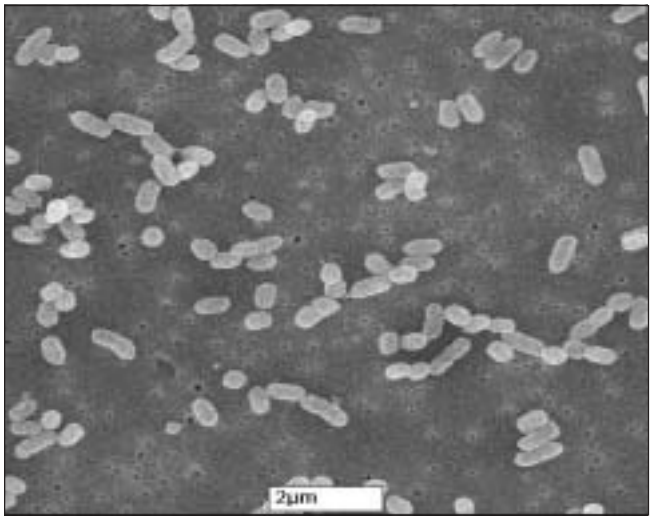


Figure 4–1: B. diminuta *on Durapore membrane*

Non-Destructive Testing

A non-destructive physical integrity test is used in place of a destructive test because a destructive test leaves the filter unfit for use. The stringent requirements of the pharmaceutical industry dictate that non-destructive tests for filter integrity be used on each application. For the integrity test to be meaningful, it must be correlated with bacterial retention tests.

Two common non-destructive integrity tests are bubble point test and diffusion test. The bubble point integrity test has a direct correlation to bacterial retention, while diffusion testing has an indirect correlation.

Bubble Point Test

The bubble point test is based on the fact that liquid is held in the pores of the filter by surface tension and capillary forces. Bubble point is the pressure where gas displaces liquid from the largest set of filter pores and flows rapidly (bulk flow) through the filter. The theoretical equation describing bubble point is:

$$P = \frac{4\ k \cos(\theta)\ \sigma}{d}$$

P = bubble point pressure
d = pore diameter
k = shape correction factor
θ = liquid-solid contact angle
σ = surface tension

Other factors that affect bubble point measurements are membrane structure, temperature, wetting fluid and degree of wetting.

NOTE: The most common cause of pre-use integrity test failures is insufficient wetting.

When performing a bubble point test, you must specify the following parameters:

- Filter type
- Wetting fluid
- Temperature of system (room, fluid, and filter)

Diffusion Test

A diffusion test involves applying a differential gas pressure below the bubble point. Gas molecules migrate through the water filled pores of the membrane following Fick's Law of Diffusion. The gas diffusional flow rate for a filter is proportional to the differential pressure and the total surface area of the filter. At a pressure of approximately 80% of the minimum bubble point, the gas which diffuses through the membrane is measured to determined filter's integrity. This flow is much smaller than the bulk flow associated with bubble point.

$$Q = \frac{K\,(P1\text{-}P2)\;A\rho}{L}$$

Q = diffusional flow
K = diffusivity / solubility coefficient
(P1-P2) = pressure difference across the system
A = membrane area
ρ = membrane porosity
L = effective path length

Factors that affect the measurement of diffusion are the degree to which the membrane is fully wetted, wetting fluid, gas type, and temperature.

NOTE: The most common cause of pre-use integrity test failures is insufficient wetting.

When performing a diffusion test, you must specify the following parameters:

- Filter type
- Filter surface area
- Wetting fluid
- Test gas (NOTE: Gases have varying diffusivities and solubilities)
- Temperature
- Maximum acceptable flow rate
- Test pressure

Automatic or Manual Integrity Testing

Bubble point and diffusion tests can be performed manually or with an automatic integrity tester. A manual test requires minimal equipment and is easy to perform. However, its use as a post-sterilization/pre-use integrity test is limited because manual tests require aseptic manipulations downstream of the filter.

In contrast to manual methods, automatic integrity testers rely upon upstream measurements for the determination of filter integrity. Connection and operation of these instruments does not compromise downstream sterility. These instruments eliminate operator subjectivity, provide a hard copy of the data, and may provide data storage. However, automatic integrity testers are very sensitive to small leaks and small temperature variations and require appropriate installation and operational qualification.

Users performing any integrity test should be qualified and certified. If an automatic integrity test is the user's preferred method, that user should be trained in performing manual integrity test methods so that these methods can be used as a back up should an automatic integrity tester become unavailable. The following sections describe manual methods for integrity testing.

NOTE: Millipore offers two models of automatic integrity testers, the Integritest® II series and the Integritest Exacta series instruments. Each instrument has specific features and uses different features and methods to determine filter integrity. The operation of these instruments is outside the scope of this guide. Refer to the instruction manuals supplied with your automatic integrity tester for complete information on their operation. You may also contact your Millipore representative for assistance with installation and operational qualification, calibration, service, or training for your Millipore automatic integrity testers.

Diffusion Test or Bubble Point Test?

Millipore recommends using a bubble point test when possible because bubble point is a function of pore size and is directly correlated to bacterial retention. You can determine the bubble point manually on filters as small as a 47 mm disk and up. Manual bubble point determination is typically limited to gas flow rates of up to 100 mL/min. Any system with a diffusional flow rate greater than 100 mL/min makes a distinction between diffusional flow and bulk flow difficult. Diffusion flow specifications are directly proportional to surface area. Typically filters with surface area less than 2 ft^2 do not have a diffusion specification because the diffusional flow is too small to accurately measure.

Tables 4–1 and 4–2 show the diffusion rate and bubble point specifications for Millipore cartridges and capsules.

Table 4–1: Hydrophilic Durapore Cartridges—Integrity Testing Specifications at 23 °C

Product Designation	Catalogue Number	Integrity Test Type	Product Specifications	Test Gas Test Pressure	Test Fluid
Durapore 0.22 µm 5" to 30" Cartridges	CVGL----- 0.22 µm CV19----- CV06----- CV03----- with single Milligard layer	Bubble Point	≥ 50.0 psig (3450 barg) ≥ 18.5 psig (1280 mbar)	Air Nitrogen	Water 70/ 30 IPA/ Water
		Diffusion	5" : ≤ 6.6 cc/ min 10" : ≤ 13.3 cc/ min 20" : ≤ 26.6 cc/ min 30" : ≤ 39.9 cc/ min	Air 40 psig (2760 mbar)	Water
Durapore 0.22 µm 10" to 30" Cartridges with Double Milligard Layer	CVSC----- CVSS----- CVSX----- with double Milligard layer	Bubble Point	≥ 50.0 psig (3450 barg)	Air	Water
		Diffusion	10" : ≤ 10.8 cc/ min 20" : ≤ 21.6 cc/ min 30" : ≤ 32.4 cc/ min	Air 40 psig (2800 mbar)	Water
Charged Durapore 0.22 µm 10" to 30" Cartridges	CCGL----- 0.22 µm	Bubble Point	≥ 40 psig (2760 mbar)	Air	Water
		Diffusion	10" : ≤ 10 cc/ min 20" : ≤ 20 cc/ min 30" : ≤ 30 cc/ min	Air 30 psig (2070 mbar)	Water
Durapore 0.1 µm 5" to 30" Cartridges	CVVL----- 0.1 µm	Bubble Point	≥ 70 psig (4830 mbar)	Air	Water
		Diffusion	5" : ≤ 10 cc/ min 10" : ≤ 20 cc/ min 20" : ≤ 40 cc/ min 30" : ≤ 60 cc/ min	Air 56 psig (3860 mbar)	Water
Durapore 0.45 µm 10" to 30" Cartridges	CVHL----- 0.45 µm	Bubble Point	≥ 28 psig (1930 mbar)	Air	Water
		Diffusion	10" : ≤ 15 cc/ min 20" : ≤ 30 cc/ min 30" : ≤ 45 cc/ min	Air 22.0 psig (1520 mbar)	Water
0.65 µm 10" to 30" Cartridges	CVDR----- 0.65 µm	Bubble Point	≥ 14 psig (970 mbar)	Air	Water
		Diffusion	10" : ≤ 8 cc/ min 20" : ≤ 16 cc/ min 30" : ≤ 24 cc/ min	Air 9.0 psig (620 mbar)	Water
Optiseal 0.22 µm Cartridges	LAGL 0.22 µm	Bubble Point	≥ 50.0 psig (3450 mbar) ≥ 18.5 psig (1280 mbar)	Air Nitrogen	Water 70/ 30 IPA/ Water
		Diffusion	≤ 5.0 cc/ min	Air 40 psig (2800 mbar)	Water

Table 4–1: Hydrophilic Durapore Cartridges—Integrity Testing Specifications, continued

Product Designation	Catalogue Number	Integrity Test Type	Product Specifications	Test Gas Test Pressure	Test Fluid
Charged Optiseal 0.22 µm Cartridges	LCGL----- 0.22 µm	Bubble Point	≥ 40 psig (2759 mbar)	Air	Water
		Diffusion	≤ 4.0 cc/ min	Air 30 psig (2069 mbar)	Water
Optiseal 0.1 µm Cartridges	LAVL----- 0.1 µm	Bubble Point	≥ 70.0 psig (4800 mbar)	Air	Water
		Diffusion	≤ 7.0 cc/ min	Air 56 psig (3900 mbar)	Water
Optiseal 0.45 µm Cartridges	LAHL----- 0.45 µm	Bubble Point	≥ 28 psig (1931 mbar)	Air	Water
		Diffusion	≤ 4.0 cc/ min	Air 22 psig (1517 mbar)	Water
Millidisk Stacked Disk Cartridges	MCGL----- 0.22 µm	Bubble Point	≥ 50.0 psig (3450 mbar) ≥ 18.5 psig (1280 mbar)	Air Nitrogen	Water 70/ 30 IPA/ Water
	MCVL----- 0.1 µm	Bubble Point	≥ 70.0 psig (4830 mbar)	Air	Water
	MCHL----- 0.45 µm	Bubble Point	≥ 26.0 psig (1800 mbar)	Air	Water
	MCSL----- 5.0M µm	Bubble Point	≥ 2.0 psig (140 mbar)	Air	Water

Table 4–2: Hydrophilic Durapore Capsules—Integrity Testing Specifications at 23 °C.

Product Designation	Catalogue Number	Integrity Test Type	Product Specifications	Test Gas Pressure**	Test Fluid
Opticap 0.22 µm 4" to 10" Capsules	Non-Sterile KVGL0----- 0.22 µm	Bubble Point	≥ 50.0 psig (3450 mbar) ≥ 18.5 psig (1280 mbar)	Air Nitrogen	Water 70/ 30 IPA/ Water
		Diffusion for 10" Capsule*	≤ 13.3 cc/ min	Air 40 psig (2760 mbar)	Water
Opticap 0.22 µm 4" to 10" Capsules	Gamma Stable KVGLG----- Gamma Sterilized KVGLS	Bubble Point	≥ 50.0 psig (3450 mbar) ≥ 18.5 psig (1280 mbar)	Air Nitrogen	Water 70/ 30 IPA/ Water
		Diffusion for 10" Capsule*	≤ 14.0 cc/ min	Air 40 psig (2760 mbar)	Water
Opticap 0.1 µm 4" to 10" Capsules	Non-Sterile KVVL0----- 0.1 µm	Bubble Point	≥ 70.0 psig (4828 mbar)	Air	Water
		Diffusion for 10" Capsule*	≤ 20 cc/ min	Air 56 psig (3862 mbar)	Water
Opticap 0.1 µm 4" to 10" Capsules	Gamma Stable KVVLG----- Gamma Sterilized KVVLS-----	Bubble Point	≥ 70.0 psig (4828 mbar)	Air	Water
		Diffusion for 10" Capsule*	≤ 21.1 cc/ min	Air 40 psig (2760 mbar)	Water
Millipak Stacked Disk Capsules	MPGL----- 0.22 µm	Bubble Point	≥ 50.0 psig (3450 mbar) ≥ 18.5 psig (1280 mbar)	Air Nitrogen	Water 70/ 30 IPA/ Water
	MPVL----- 0.1 µm	Bubble Point	≥ 70.0 psig (4800 mbar)	Air	Water
	MPHL----- 0.45 µm	Bubble Point	≥ 26.0 psig (1800 mbar)	Air	Water
	MPSL----- 5.0 µm	Bubble Point	≥ 2.0 psig (140 mbar)	Air	Water

* Diffusion tests are not recommended for devices less than 2 ft^2.
**Test pressure specified for the Diffusion Test.

NOTE: The specifications supplied in this document are for reference purposes only. Always refer to the certificate of quality for the lot of product in use for current information.

Considerations for When to Perform Pre-use Integrity Tests

There are two options for pre-use integrity testing: pre- and post-sterilization. Either option is a good practice for a number of reasons:

- Prevents batch processing with a non-integral filter
- Alerts operator to a problem
- Ensures proper installation
- Verifies unit was not damaged during shipping

In addition, post-sterilization integrity tests check for damage during the sterilization process. However you must maintain system sterility during filter wetting and integrity testing steps. You may find an automatic integrity tester very useful in post-sterilization integrity testing.

Pre-Integrity Test Wetting of Hydrophilic Durapore Cartridges and Capsules

You must wet the membrane completely before starting the test. Complete wetting is critical to properly measure the diffusion rate and the bubble point pressure.

Wetting Water Quality

The water used for wetting prior to integrity testing should be reverse osmosis (RO), deionized (DI), or USP Water for Injection (WFI) at ambient temperature (impurities can affect the integrity test results). An alternative wetting fluid may be necessary in some cases. Alternative wetting fluids must be validated prior to using.

Wetting Methods

There are two methods for wetting membrane filters: direct flow using a pressure tank or recirculation using a peristaltic pump. Wetting using a pressure tank is the most efficient and preferred method. Wetting using a peristaltic pump in a recirculating mode reduces the amount of water (or other validated wetting fluid) required during the wetting procedure.

Wetting Setup with a Pressure Tank

This wetting procedure is for cartridges and capsules. (See Figure 4-2.) The figure illustrates the cartridge wetting process. However, you could easily replace the cartridge/housing surrounded by dashes with a capsule filter.

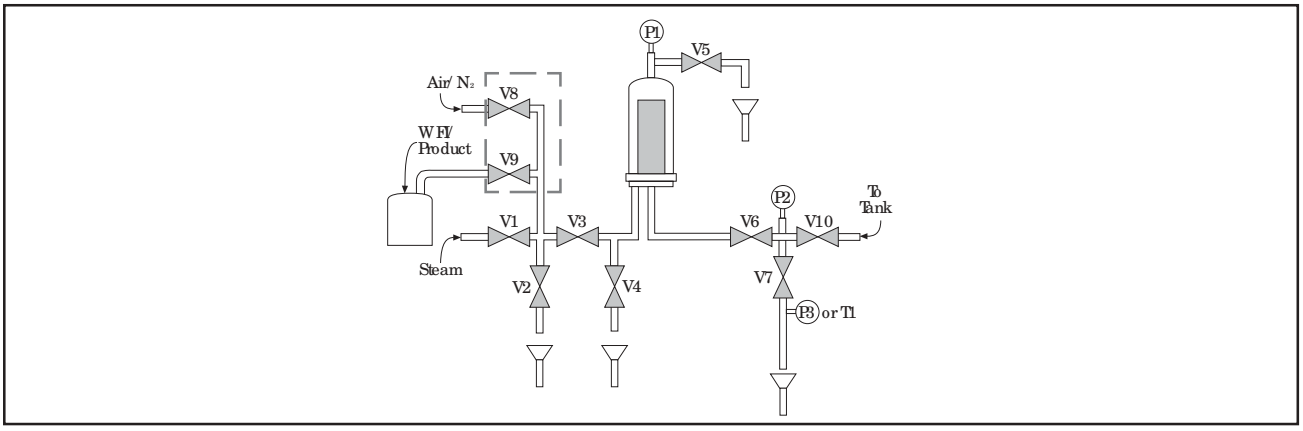


Figure 4–2: Typical sterile filter cartridge and housing assembly for pressure tank wetting

Precautions

Before starting the procedure, check the following:

- The proper filter has been selected; confirm pore size and catalogue number
- Filter is installed correctly in the housing (See Chapter 2 for details on proper filter installation.)
- All valves are closed
- Water (or validated alternate wetting fluid) can deliver at least 1 liter/minute per ft^2 of effective filter surface area at 20 psig (1.4 bar). This can be supplied by using a pressure vessel or a peristaltic pump (See V9 in Figure 4-2).

Wetting Procedure with a Pressure Tank (most efficient and preferred method)

Monitor and control the temperature of the wetting fluid and the filter/system to the temperature specified for the particular diffusion or bubble point test you want to perform. Tests performed at temperatures other than those recommended can affect the results of both the diffusion and the bubble point tests.

1. Clear a path for the wetting fluid to enter the system and clear a path for air to exit (Open V3 and V5).
2. Allow the wetting fluid to enter the filter. (Slightly crack open V9.)
3. Ensure that all gas is purged. When you can see a steady flow of the wetting fluid and no gas exiting V5, close V5.

   NOTE: Trapped air can prevent the membrane from becoming fully wet; this can cause improper measurement of the diffusion rate and the bubble point test pressure.
4. Increase the pressure on the feed side of the filter to a minimum of 20 psig (1.4 bar). (A pressure of 40 psig (2.8 bar) is ideal. Fully open V9.)

   NOTE: Do not exceed the maximum pressure rating for the filter unit.
5. Maintain this pressure for at least 1 minute to dissolve any residual gas within the filter to ensure complete membrane wetting.
6. Open outlet valve(s) until the wetting fluid flow is approximately 1 L/min per ft^2 of effective filter surface area. (Open V6, and crack open and throttle V7). See Table 4-3 for wetting conditions.

   NOTE: The filtrate-side pressure increases because only a small differential pressure is required to achieve 1 L/min per ft^2.
7. Shut off wetting fluid supply (V9) after 5 minutes. Allow the feed-side pressure to decay to zero psig, then close all valves. You may now perform an integrity test on the filter.

Table 4–3: Specified Wetting Conditions Using a Pressure Tank or Peristaltic Pump

Filter Type	Water Flow Rate (L/ min)	Wetting Volume (L) for 5 min pressure	Required volume (L) in recirculation peristaltic pump
Millidisk 10	0.5	3	1
Millidisk 20	1.0	5	2
Millidisk 30	1.5	8	2
Millidisk 40	2.0	10	3
Millipak 20	0.1	1	1
Millipak 40	0.2	1	1
Millipak 60	0.4	2	1
Millipak 100	0.5	3	1
Millipak 200	1	5	2
Optiseal/ Opticap	2	10	3
Durapore 5”	3.5	18	5
Durapore 10”	7	35	8
Durapore 20”	14	70	12
Durapore 30”	21	105	15

Hydrophilic filters wet at a minimum flow rate of approximately 1 Lpm/ ft² of effective filtration area for 5 minutes.

Wetting Setup with a Peristaltic Pump

This wetting procedure is for cartridges and capsules. (See Figure 4-3.) The figure illustrates the cartridge wetting process. However, you could easily replace the cartridge/housing with a capsule filter.

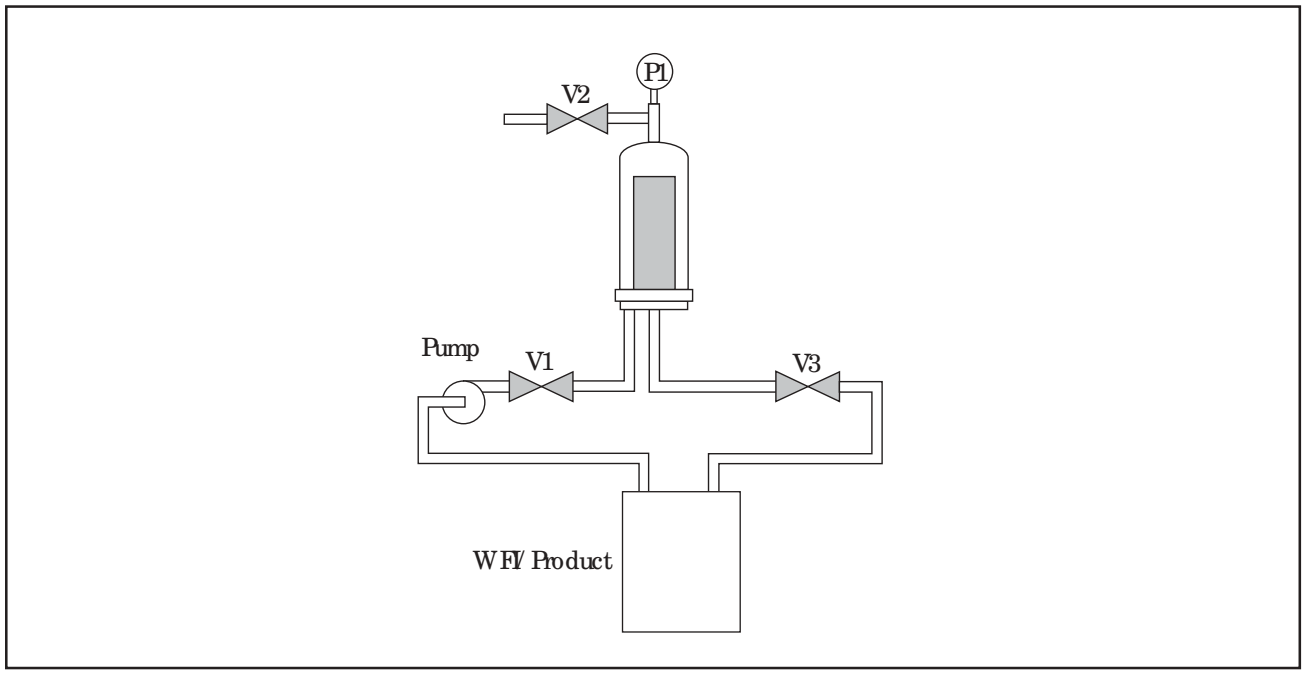


Figure 4-3: Typical sterile filter cartridge and housing assembly for recirculation wetting using a peristaltic pump

Precautions

Before starting the procedure, check the following:

- The proper filter has been selected; confirm pore size and catalogue number
- Filter is installed correctly in the housing (See Chapter 2 for details on proper filter installation.)
- All valves are closed

Wetting Procedure with a Peristaltic Pump

Monitor and control the temperature of the wetting fluid and the filter/system to the temperature specified for the particular diffusion or bubble point test you want to perform. Tests performed at temperatures other than those recommended can affect the results of both the diffusion and the bubble point tests.

1. Ensure that all valves are closed.
2. Set the peristaltic pump at the correct setting and start the pump.
3. Open the vent valve (V2)
4. Gradually open the feed-side valve (V1).
5. Ensure that all gas is purged. When you can see a steady flow of the wetting fluid and no gas exiting V2, close V2.

   NOTE: Trapped air can prevent the membrane from becoming fully wet; this can cause improper measurement of the diffusion rate and the bubble point test pressure.
6. Stop the pump and continue to maintain pressure at least 1 minute to dissolve any residual gas within the filter to ensure complete membrane wetting.
7. Restart the pump and open the filtrate-side valve (V3).
8. Adjust the peristaltic pump until the differential pressure (P1-P2) is approximately 3 psig (200 mbar)
9. Recirculate the wetting fluid through the filter at approximately 1 L/min per ft2 of effective filter surface area. See Table 4-3 for the recommended flow rate and minimum volume of wetting fluid necessary to wet the filter in recirculation mode.
10. Shut off the pump after 5 minutes of recirculation. Allow the feed-side pressure to decay to zero psig, then close all valves. You may now perform an integrity test on the filter.

Bubble Point Testing of Hydrophilic Durapore Cartridges and Capsules — Manual Method

Before starting the procedure, ensure that the proper gas type is supplied for the test (air, nitrogen, etc.)

1. Allow excess wetting fluid to flow out of the down stream side of the system. (Open V8, V3, V6, and V7.) Refer to Figure 4–4.
2. Set gas pressure regulator to 5 psig. Hold until the water has stopped flowing from the outlet port.

   NOTE: Look for rapid continuous bubbling at test apparatus attached to Valve 7 at this time. If none occurs, continue to the next step. Rapid bubbling at this time may be due to insufficient wetting or improper filter installation. Check the filter installation and repeat the steps listed in the previous wetting procedure if you see rapid bubbling.
3. Increase gas pressure regulator to 80% of the bubble point test pressure specification. (See Tables 4–1 and 4–2 for details.)
4. Allow the system to equilibrate for 5 minutes.
5. Increase the pressure in 1 psi increments. Wait 10 seconds in between increases to allow the system to stabilize.
6. Record the pressure as the bubble point pressure when the slow steady flow of bubbles increases at the outlet of the filter to rapid bubbling.

Bubble Point Testing of Hydrophilic Durapore Cartridges and Capsules, continued

7. Do one of the following:
   - If the bubble point value is below the specification (a failing bubble point), close V8, allow pressure P1 to decay to zero, and proceed to step 8.
   - If the value is equal to or above the specification (a passing bubble point), proceed with the sterile filtration process in Chapter 5.

   NOTE: To ensure that the integrity test failure is not due to insufficient wetting, prepare to rewet the system at higher pressure and increase contact time.
8. Check the following (if the bubble point value is below the specification):
   - All connections and valves for potential leaks.
   - Ensure the filter is installed properly.
   - Ensure the temperature is stable and within temperature specification.
   - Close all valves.
9. Rewet filter in preparation for re-test as follows: Clear a path for wetting fluid to enter, and clear a path for air to exit.
10. Allow the wetting fluid to enter the filter. (Slightly crack open V9.)
11. Ensure that all gas is purged. When you can see a steady flow of water and no gas exiting V5, close V5.
12. Increase the pressure on the feed side of the filter to at least 20 psi. (A pressure of 40 psi is ideal. Fully open V9.)

    NOTE: Do not exceed the maximum pressure rating for the filter unit.
13. Continue to maintain this pressure for at least 1 min to dissolve any residual gas within the filter and ensure membrane wetting.
14. Open outlet valve(s) until WFI flow is approximately 1 L/min per ft^2. (Open V6, and crack open and throttle V7.)

    NOTE: The filtrate side pressure increases because only a small differential pressure is required to achieve 1 L/min per ft^2.
15. Rewet using the conditions specified in Table 4–3.
16. Perform Bubble Point Retest: Repeat steps 1 through 8. If your test fails, save the filter and contact Millipore Technical Service for assistance.

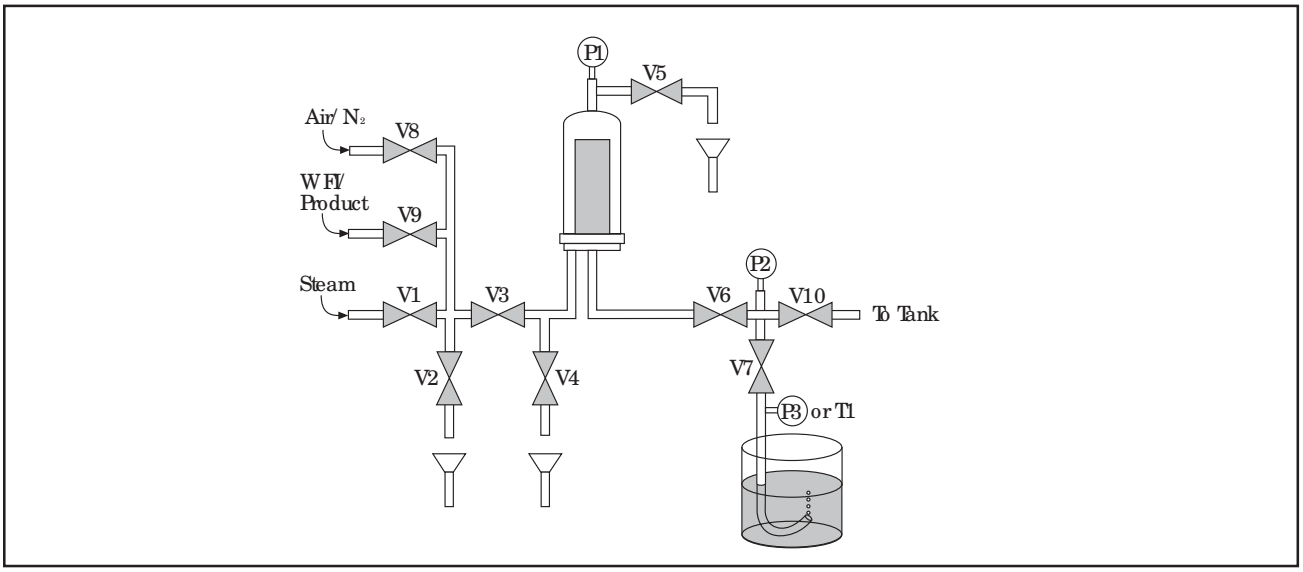


Figure 4–4: Typical sterile filter cartridge and housing assembly for bubble point test

Diffusion Integrity Testing of Hydrophilic Durapore Cartridges and Capsules

Diffusion Integrity Testing Procedure

Before starting the procedure, ensure that the proper gas type is supplied for the test (air, nitrogen, etc.).

1. Allow excess water to flow out of the down stream side of the system. (Open V8, V3, V6, and V7.) Refer to Figure 4–5.
2. Set gas pressure regulator to 5 psig. Hold until wetting fluid has stopped flowing from the outlet port.

   NOTE: Look for rapid continuous bubbling at this time. If none occurs, continue to the next step. Rapid bubbling at this time may be due to insufficient wetting or improper filter installation. Check the filter installation and repeat the steps listed in the previous wetting procedure if you see rapid bubbling.
3. Increase gas pressure regulator to diffusion test pressure specification. (See Tables 4–1 and 4–2 for details.)
4. Allow the system to equilibrate for 5 minutes.
5. Measure the diffusion flow rate with a flow meter or a water filled inverted graduated cylinder. (See Figure 4–5.)
6. Hold the open end of tubing attached to system outlet under the graduated cylinder. (The gas diffusing through the filter displaces the wetting fluid in the graduate.) Time for 1 minute. You can read the diffusion rate in cc/min directly from the cylinder.
7. Do one of the following:
   - If the diffusional flow rate is greater than the specification (a failing diffusion rate), proceed to step 8.
   - If the value is equal to or below the specification (a passing diffusion rate), proceed with the sterile filtration process in Chapter 5.

   NOTE: To ensure that the integrity test failure is not due to insufficient wetting, prepare to rewet the system at higher pressure and increased contact time.

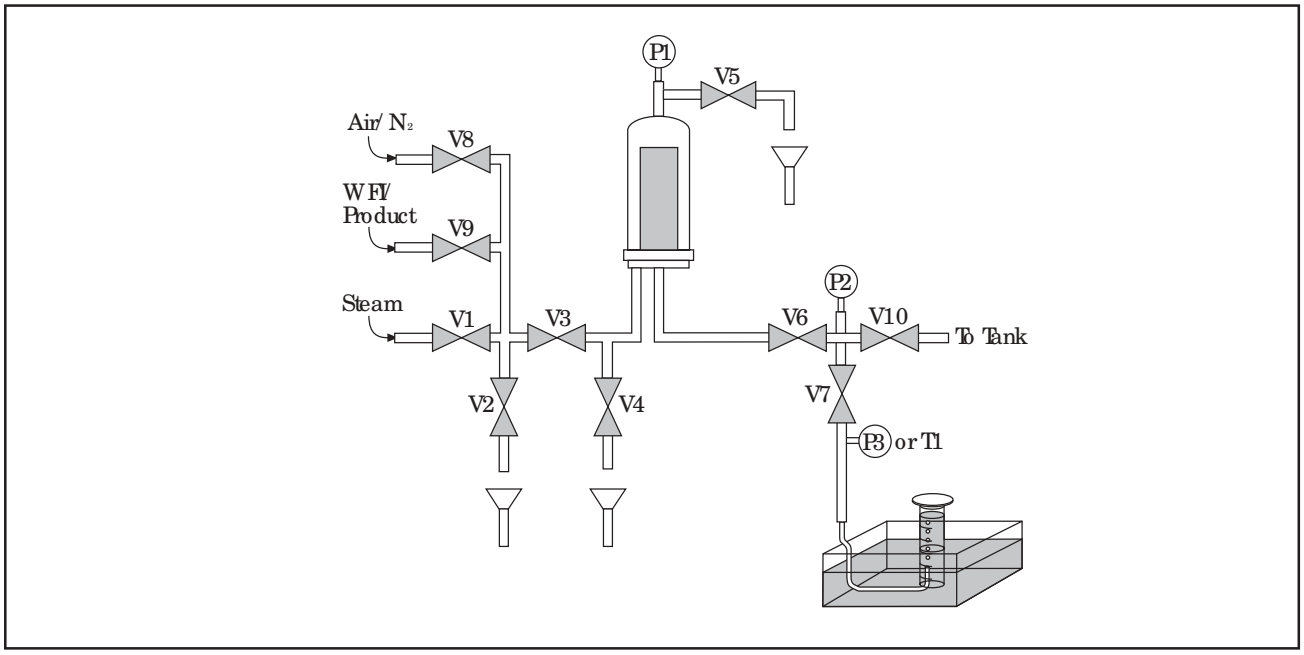


Figure 4–5: Typical sterile filter cartridge and housing assembly for diffusion test

Diffusion Integrity Testing Procedure, continued

8. Check the following:
   - All connections and valves for potential leaks.
   - Ensure the filter is installed properly.
   - Ensure the temperature is stable and within temperature specification.
   - Close all valves.
9. Clear a path for wetting fluid to enter, and clear a path for air to exit.
10. Allow the wetting fluid to enter the filter. (Slightly crack open V9.)
11. Ensure that all gas is purged. When you can see a steady flow of water and no gas exiting V5, close V5.
12. Increase the pressure on the feed side of the filter to at least 20 psi. (A pressure of 40 psi is ideal. Fully open V9.)

    NOTE: Do not exceed the maximum pressure rating for the filter unit.
13. Continue to maintain this pressure for at least 1 min to dissolve any residual gas within the filter and ensure membrane wetting.
14. Open outlet valve(s) until wetting fluid flow is approximately 1 L/min per ft^2. (Open V6, and crack open and throttle V7.)

    NOTE: The filtrate side pressure increases because only a small differential pressure is required to achieve 1 L/min per ft^2.
15. Rewet using the conditions specified in Table 4–3.
16. Repeat steps 1 through 8. If your test fails, save the filter and contact Millipore Technical Service for assistance.

Additional Integrity Testing Literature

Contact Millipore to obtain the following literature for more details on Integrity Testing

- Technical Note (Integrity Testing of Sterilizing Membrane Filters) Lit. No. TN012 Rev. -06/91
- Technical Brief (Filter Integrity Test Methods) Lit. No. TB039 Rev A 05/99
- Reprint from Pharmaceutical Technology, September 1989 (Principles of Integrity-Testing Hydrophilic Microporous Membrane Filters, Part I) Lit. No. TB036
- Reprint from Pharmaceutical Technology, September 1989 (Principles of Integrity-Testing Hydrophilic Microporous Membrane Filters, Part II) Lit. No. TB036

Integrity Testing, Training, and Certification

Operators who need to perform integrity tests need proper training. Millipore offers a course that teaches the current theories and methods for filter integrity testing. This course allows operators to meet CGMP training requirements.

Some of the key points covered in this course are:

- Perform and master bubble point, diffusion, and automatic integrity testing methods.
- Run integrity tests on hydrophobic and hydrophilic filter devices.
- Practice manual and automatic test methods and techniques.
- Reinforce all the classroom material through comprehensive laboratory sessions.
- Learn methods from Millipore integrity testing and process filtration experts.
- Attend classes that allow limited class sizes to ensure individual attention.

Contact your Millipore Application Specialist for more information.

Chapter 5

Guidelines for Sterile Filtering and Post-Use Integrity Testing

Introduction

This chapter provides information on properly performing:

- Sterile filtration of your process fluid
- A post-filtration integrity test to release the sterile filtered product for use

Guidelines for Sterile Filtering and Post-Use Integrity Testing

Once you reach this chapter on hydrophilic Durapore use, you should have already inspected the filter out of the box, installed it for use, sterilized it, cooled it under positive pressure, wetted it for integrity testing, post-sterilization integrity tested it, drained it, and are now ready to use it. The previous chapters in this manual define the basic guidelines for use. When you begin your filtration, slowly wet the filter at low pressure and purge all air. This ensures that all of the effective membrane area is used and that the membrane is fully wetted prior to the post-use integrity test.

NOTE: Wetting the membrane completely before the start of the integrity test is critical to properly measuring the diffusion rate and the bubble point pressure because trapped air can prevent the membrane from becoming fully wet. (See Chapter 4, "Pre-Use Integrity Testing of Hydrophilic Durapore Cartridges and Capsules" for details.)

Post-Filtration Integrity Testing of Cartridges and Capsules

There are two types of post-use integrity testing: water based and product based. The choice depends on the nature of the product you want to filter. If all of the product components can be effectively flushed from the filter, then use a water based integrity specification.

Some typical fluids used for flushing include:

- WFI
- Hot WFI (80 °C)
- Alcohol or alcohol/water solutions.

However, some products leave residual components on the filter that affect the measured integrity test value. In some cases, even rigorous membrane flushing cannot remove the residual components. In these cases, you need to establish a product based integrity test specification. Millipore's Access Services can help you establish this value. To be valid, the product based integrity test values must be reproducible.

Another option is to flush the filter with a 70/30 IPA/Water reference solution. Millipore sterilizing grade (0.22 µm) filters have a bubble point specification of 18.5 psig for a 70/30 IPA reference solution. See the following procedure (Part One and Part Two) for details on this method.

Post-Use Bubble Point Test SOP: Part One

Before starting the procedure, ensure that the proper gas type is supplied for the test (air, nitrogen, etc.)

1. Allow excess wetting solution to flow out of the down stream side of the system. (Open V8, V3, V6, and V7.) Refer to Figure 5–1.
2. Set gas pressure regulator to 5 psig. Hold until the water has stopped flowing from the outlet port.
   NOTE: Look for rapid continuous bubbling at this time. If none occurs, continue to the next step. Rapid bubbling at this time may be due to insufficient wetting or improper filter installation. Check the filter installation and repeat the steps listed in the wetting procedure described in Chapter 4 if you see rapid bubbling.
3. Increase gas pressure regulator to 80% of the bubble point specification. (If you are using a product-based bubble point test, the product specific bubble point is the bubble point specification.)

Post-Use Bubble Point Test SOP: Part One, continued

4. Allow the system to equilibrate for 5 minutes.
5. Increase the pressure in 1 psi increments, waiting 10 seconds between increases to allow the system to stabilize.
6. Record the pressure (bubble point pressure) when the slow steady flow of bubbles increases at the outlet of the filter to rapid bubbling.
7. Proceed to step 8 if the bubble point value is below the specification. If the value is equal to or above the specification, the filter is integral.

   NOTE: To ensure that the integrity test failure is not due to insufficient wetting, prepare to rewet the system at higher pressure and increased contact time.

8. Check the following:
   - All connections and valves for potential leaks.
   - Ensure filter is installed properly.
   - Ensure temperature is stable and within temperature specification.
   - Close all valves.

   NOTE: If you are using a product-based bubble point test, skip the remaining steps in this procedure. Instead, see step 8 in the next part of this procedure, "Post-use Bubble Point Test SOP: Part Two."

9. Clear a path for the wetting fluid to enter, and clear a path for air to exit. (Open V3 and V5.)
10. Allow the wetting fluid to slowly fill the feed side of housing. (Slightly crack open V9.)
11. Ensure that all gas is purged. When you can see a steady flow of water or product and no gas exiting V5, close V5.
12. Open V9 fully until the feed pressure P1 is at least 40 psi.

    NOTE: Do not exceed the maximum pressure rating for the filter unit.

13. Continue to maintain this pressure for at least 1 min to dissolve any residual gas within the filter and ensure membrane wetting.
14. Open outlet valve(s) until the wetting fluid flow is approximately 1 L/min per ft^2. (Open V6, and crack open and throttle V7.)

    NOTE: The filtrate side pressure increases because only a small differential pressure is required to achieve 1 L/min per ft^2.

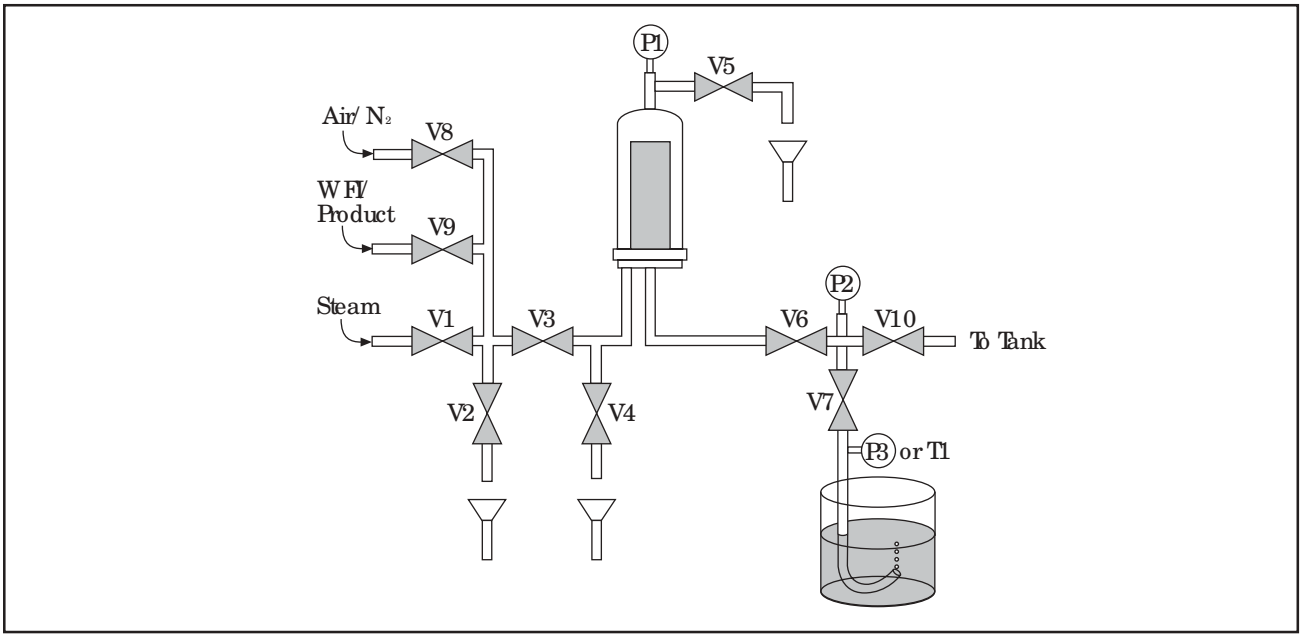


Figure 5–1: Typical sterile filter cartridge and housing assembly for bubble point test

Post-Use Bubble Point Test SOP: Part One, continued

15. Rewet using the conditions specified in Table 5–1.

Table 5–1: Specified Wetting Conditions Using a Pressure Tank or Peristaltic Pump

Filter Type	Water Flow Rate (L/ min)	Wetting Volume (L) for 5 min pressure	Required volume (L) in recirculation peristaltic pump*
Millidisk 10	0.5	3	1
Millidisk 20	1.0	5	2
Millidisk 30	1.5	8	2
Millidisk 40	2.0	10	3
Millipak 20	0.1	1	1
Millipak 40	0.2	1	1
Millipak 60	0.4	2	1
Millipak 100	0.5	3	1
Millipak 200	1	5	2
Optiseal/ Opticap	2	10	3
Durapore 5”	3.5	18	5
Durapore 10”	7	35	8
Durapore 20”	14	70	12
Durapore 30”	21	105	15

Hydrophilic filters wet at a minimum flow rate of approximately 1 Lpm/ ft² of effective filtration area for 5 minutes.

**If using the recirculation method post-use, flush product to drain and rinse properly before recirculating.*

16. Continue to the next section, “Post-Use Bubble Point Test: Part Two.”

Post-Use Bubble Point Test SOP: Part Two

1. Repeat steps 2 through 6 in the previous procedure, “Post-Use Bubble Point Test: Part One.”
2. If the bubble point value is below the specification, proceed to step 3. If the value is equal to or above the specification, the filter is integral.

   NOTE: If the filter fails two integrity tests using water, PDA Technical Report 26 allows the use of a lower surface tension reference fluid. Millipore recommends that you use a 70/30 IPA solution with Durapore. (The specification for 0.22 µm Durapore is ≥ 18.5 psig.)
3. Wet the filter using 70/30 IPA solution either by static soaking (cartridges only) the unit for a minimum of 5 minutes or by dynamic flow (capsules/cartridges) at a minimum flow rate of approximately 0.5 Lpm/ft² of effective filtration area for 5 minutes.
4. Set gas pressure regulator to 5 psig. Hold until the wetting fluid has stopped flowing from the outlet port.

   NOTE: Look for rapid continuous bubbling at this time. If none occurs, continue to the next step. Rapid bubbling at this time may be due to insufficient wetting or improper filter installation. Check the filter installation and repeat the steps listed in the wetting procedure described in Chapter 4 if you see rapid bubbling.
5. Increase gas pressure regulator to 80% of the bubble point specification for 70/30 isopropyl alcohol.
6. Allow the system to equilibrate for 5 minutes.
7. Increase the pressure in 1 psi increments, waiting 10 seconds between increases to allow the system to stabilize.
8. Record the pressure as the bubble point pressure when the slow steady flow of bubbles (diffusion only) increases at the outlet of the filter to rapid bubbling (bulk flow). If the bubble point value is still below the specification, save the filter and contact Millipore Technical Service for assistance.

Post-Use Diffusion Test

The post-use diffusion test is identical to the pre-use diffusion test defined in Chapter 4. If filter is wet with a liquid other than water, a product diffusion test should be determined. Millipore Access Services can determine a product-based diffusional flow rate specification.

Troubleshooting

This section highlights common pitfalls of integrity testing.

Symptom	Possible cause	Corrective action
Marginal bubble point or diffusion failure	Product remaining on filter (product suppression)	1. Review flushing technique 2. Perform alcohol referee test
	Temperature variations	Check fluid and environment temperature
	Insufficient wetting	Rewet at higher pressure
	Specifications	Review test specification and verify installed filter is correct
Gross Leak failure	System leaks	Check system connection, valves and filter installation.
	Non-integral filter	Inspect/replace filter
	Insufficient wetting	Rewet at higher pressure

If your tests continue to fail, save the filter and contact Millipore Technical Service for assistance.

Additional Literature on Sterile Filtration and Post-Use Integrity Testing

Contact Millipore for the following literature for more details on Sterile Filtration and Post-Filtration Integrity Testing.

- Applications Note (Establishing Product Specific Bubble Point Specifications For sterilizing-Grade (0.22 µm) Durapore Filters)
- PDA Journal of Pharmaceutical Science and Technology (Technical Report No. 26 "Sterilizing Filtration of Liquids" 1998

Appendix A

Maximum Extractables of Hydrophilic Durapore Cartridges and Capsules

Introduction

This appendix provides table information on maximum extractables for hydrophilic Durapore cartridges and capsules. It includes details on:

- Gravimetric extractables

Table A–1: Hydrophilic Durapore Cartridges—Maximum Extractables

Device	Item Number (abbreviated)*	Extractables Pre-Test Treatment**	Gravimetric Extractables less than or Equal to (mg/ unit)
Charged Durapore 10" Cartridges	CCGL-1---	Autoclave at 126 °C for 30 minutes	20
Charged Durapore 20" Cartridges	CCGL-2---	Autoclave at 126 °C for 30 minutes	40
Charged Durapore 30" Cartridges	CCGL-3---	Autoclave at 126 °C for 30 minutes	60
Durapore 5" Cartridges	CV-L-5---	Autoclave at 126 °C for 60 minutes	10
Durapore 10" Cartridges	CVDR-1PP-, CVHL-1PP-, CVGL-1, CVVL-1	Autoclave at 126 °C for 60 minutes	20
Durapore 20" Cartridges	CVDR-2PP-, CVHL-2PP-, CVGL-2---, CVVL-2---	Autoclave at 126 °C for 60 minutes	40
Durapore 30" Cartridges	CVDR-3PP-, CVHL-3PP-, CVGL-3---, CVVL-3---	Autoclave at 126 °C for 60 minutes	60
Durapore Multimedia Cartridges, 10"	CVDR-1TP-, CVHL-1TP-, CV19--TP3, CV06--TP3, CV03--TP3	Autoclave at 126 °C for 60 minutes	45
Durapore Multimedia Cartridges, 20"	CVDR-2TP-, CVHL-2TP- CV19--TP3-, CV06--TP3, CV03--TP3	Autoclave at 126 °C for 60 minutes	90
Durapore Multimedia Cartridges, 30"	CVDR-3TP-, CVHL-3TP- CV19--TP3-, CV06--TP3, CV03---TP3	Autoclave at 126 °C for 60 minutes	135
Millidisk 10 Cartridges	MC-L10---	Autoclave at 126 °C for 60 minutes	2.5
Millidisk 20 Cartridges	MC-L20---	Autoclave at 126 °C for 60 minutes	5.0
Millidisk 30 Cartridges	MC-L30---	Autoclave at 126 °C for 60 minutes	7.5
Millidisk 40 Cartridges	MC-L40---	Autoclave at 126 °C for 60 minutes	10
Optiseal Charged Durapore Cartridges	LCGL04---	Autoclave at 126 °C for 30 minutes	15
Optiseal Cartridges w/ Durapore Membrane	LAGL04---, LAVL04---	Autoclave at 126 °C for 30 minutes	10
Optiseal Multimedia Cartridges w/ Durapore Membrane	LAHL--TP-	Autoclave at 126 °C for 30 minutes	15

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Pre-test treatment conditions described in this table are not intended as a substitute for filter sterilization validation. The user is responsible for conducting an on-site filter sterilization validation study.

Table A–2: Hydrophilic Durapore Capsules—Maximum Extractables

Device	Item Number (abbreviated)*	Extractables Pre-Test Treatment**	Gravimetric Extractables less than or equal to (mg/ unit)
Millipak 60, Non-Sterile Capsules	MP-L06---	Autoclave at 123 °C for 90 min	2.0
Millipak 100, Non-Sterile Capsules	MP-L1----	Autoclave at 123 °C for 90 min	2.5
Millipak 200, Non-Sterile Capsules	MP-L2----	Autoclave at 123 °C for 90 min	5.0
Millipak 20, Pre-Sterilized by Gamma Capsules	MP-L--G--	Irradiation	1.0 mg after a 200 mL Flush
Millipak 40, Pre-Sterilized by Gamma Capsules	MP-L--G--	Irradiation	1.5 mg after a 200 mL Flush
Millipak 60, Pre-Sterilized by Gamma Capsules	MP-L--G--	Irradiation	2.0 mg after a 200 mL Flush
Millipak 100, Pre-Sterilized by Gamma Capsules	MP-L-G---	Irradiation	2.5 mg after a 200 mL Flush
Millipak 200, Pre-Sterilized by Gamma Capsules	MP-L-G---	Irradiation	5.0 mg after a 200 mL Flush
Opticap 10" Capsules, Non-Sterile	KPHL01---, KVGL01---, KVVL01---	Autoclave at 126 °C for 60 min	25
Opticap 10" Capsules, Non-Sterile, Gamma Compatible	KVGLG1---, KVVLG1---	N/ A	25
Opticap 10" Capsules, Pre-Sterilized by Gamma	KVGLS4, KVVLS4	Irradiation	10 mg after a 500 mL Flush
Opticap 4" Capsules, Non-Sterile	KVG04---	Autoclave at 126 °C for 30 min	10
Opticap 4" Capsules, Non-Sterile, Gamma Compatible	KVGLG4---, KVVLG4---	N/ A	10
Opticap 4" Capsules, Pre-Sterilized by Gamma	KVGLS1---, KVVLS1---	Irradiation	25 mg after a 1000 mL Flush
Opticap 4" Multimedia Capsules, Non-Sterile	KV0304---, KV0604---, KV1904---	Autoclave at 123 °C for 30 min	15
Opticap 4" Multimedia Capsules, Non-Sterile	KVSC04---, KVSS04---, KVSX04---	Autoclave at 123 °C for 30 min	20
Opticap 4" Multimedia 0.45 µm Capsules, Non-Sterile	KVHL01---	Autoclave at 121 °C for 30 min	15

* Refer to the Millipore catalogue or www.millipore.com for the full catalogue number of the device configuration you are interested in. These abbreviated numbers are for quick reference only.

** Pre-test treatment conditions described in this table are not intended as a substitute for filter sterilization validation. The user is responsible for conducting an on-site filter sterilization validation study.