High Sensitivity Binary Gas Integrity Test for Viresolve® Pro Devices

The Innovative Parvovirus Clearance Solution

ABSTRACT

A novel non-destructive integrity test for microporous and ultraporous membranes has been developed that is far more sensitive to detecting defects than a conventional gas-liquid diffusion test. The test uses a binary gas mixture and is based on the principle of differing gas permeabilities through the liquid layer that results in a concentration enhancement of the faster permeating gas. In an integral membrane, the permeate composition can be predicted based on the transport properties of the gases permeating through the liquid layer and the known operating conditions. A deviation from the expected concentration is an indication of the presence of a defect or open pores. Unlike the gas-liquid diffusion test, the binary gas test has low sensitivity to membrane porosity, liquid layer thickness, and membrane area. Consequently, integral devices will exhibit a relatively narrow range of integral values resulting in a superior defect signal-to-noise ratio. The binary gas integrity test method was applied to the Viresolve Pro device and was demonstrated to provide a significantly higher level of virus retention assurance compared to the air-water diffusion test. Binary gas testing has been implemented as a 100% quality assurance test for Viresolve® Pro devices.

BACKGROUND

Unique Technology

Asymmetric PES Membrane
- Patented asymmetric membrane
- Robust viral clearance
- High capacity and flux
- Caustic stable

Novel Device Formats
- Scalable devices design
- Disposable flow path
- Designed to enable integrity testing
- Manufacturing process design

Integrity and Performance
- Testing
- LRV/capacity assays using model viruses and proteins
- Liquid-liquid porometry tests
- ***Patented Binary Gas Test***

Building Assurance Test by Test

No one does more than Millipore to help assure virus filter performance and compliance

- End-User Validation and Testing
- Device 100% Tests
- Device Release Tests
- Membrane Release Tests
- Viresolve Pro Process & Product Validation

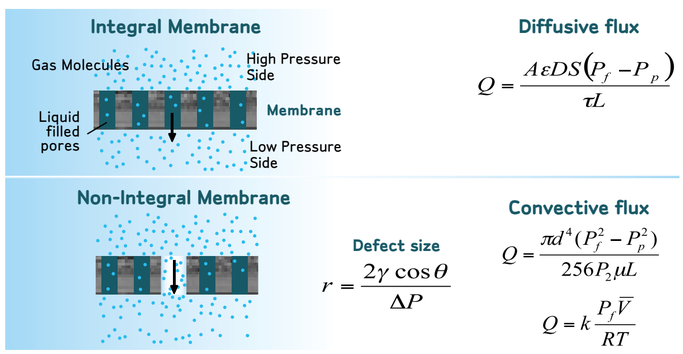
Integrity Test Objective

Purpose of Integrity test is to detect the presence of oversized pores or defects that can compromise the retention capability of a filter

- Must correlate to bacteria/virus retention or retention shortfall
- Must be non-destructive (except post-use tests)
- Ideally provides Log Reduction Value (LRV) assurance consistent with product claim

THEORY

Conventional Gas-Liquid Diffusion Test



Diffusive flux

$$Q = \frac{A\varepsilon DS(P_f - P_p)}{\tau L}$$

Defect size

$$r = \frac{2\gamma\cos\theta}{\Delta P}$$

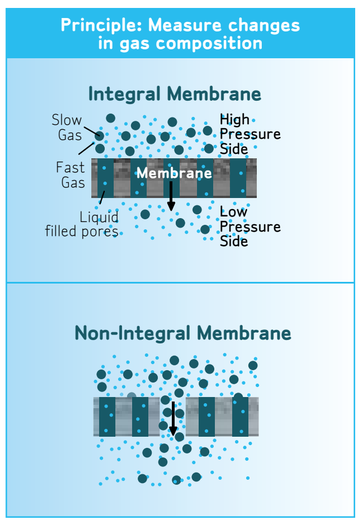
Convective flux

$$Q = \frac{\pi d^4 (P_f^2 - P_p^2)}{256 P_2 \mu L}$$

$$Q = k\frac{P_f \overline{V}}{RT}$$

- Air/water test used commonly to test virus filters
- Sufficient and appropriate as an end-user test
- Test sensitivity limitation: convective flux vs. background diffusive flux noise

Viresolve Pro Solution Includes a Novel Binary Gas Test



- Ratio of permeabilities of each component:

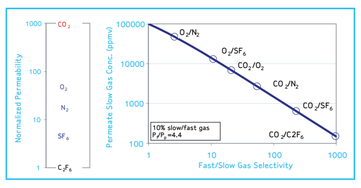
$$n_a = \frac{A\varepsilon D_a S_a [y_{a,f} P_f - y_{a,p} P_p]}{\tau L} \quad \text{Component a}$$

$$n_b = \frac{A\varepsilon D_b S_b [y_{b,f} P_f - y_{b,p} P_p]}{\tau L} \quad \text{Component b}$$

$$\frac{y_p}{1-y_p} = \frac{\phi(y_f - \mathrm{Pr}\, y_p)}{1 - y_f - \mathrm{Pr}(1-y_p)} \qquad \phi = \frac{D_a S_a}{D_b S_b} \qquad \mathrm{Pr} = \frac{P_p}{P_f}$$

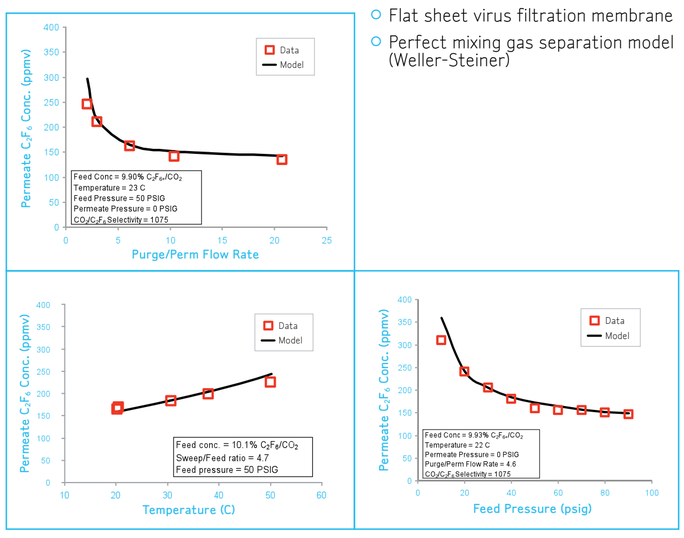
- A small defect will "contaminate" the permeate, resulting in a concentration difference that is easily detected
- Binary Gas Test provides higher sensitivity:
  - No dependence on membrane structural properties or movement/compression
  - Less variability than in flow measurements
- Allows integrity testing of micro devices

Binary Gas Pair Selection



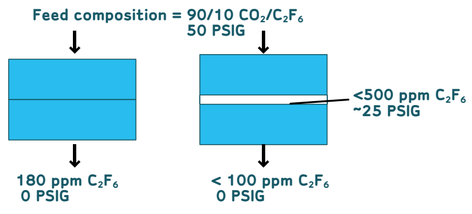
- Selected gas pair and liquid: 90/10 CO_2/C_2F_6 in water
- High sensitivity to defects
- Easy and accurate composition measurement
- High diffusive flow rate of CO_2 through water enables integrity testing of small devices

Effect of Pressure, Temperature, and Purge Ratio on Permeate Composition



- Flat sheet virus filtration membrane
- Perfect mixing gas separation model (Weller-Steiner)

Effect of Staging on Membrane Gas Separation

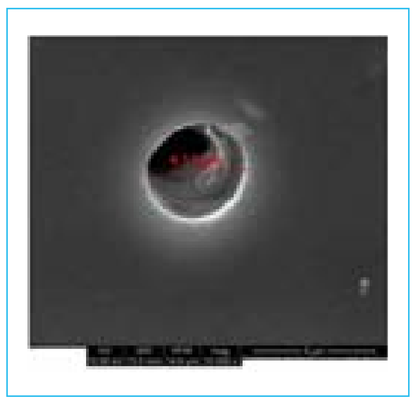


- Concentration depends only on pressure ratio (not additive)
- Flow rate depends only on pressure difference (additive)

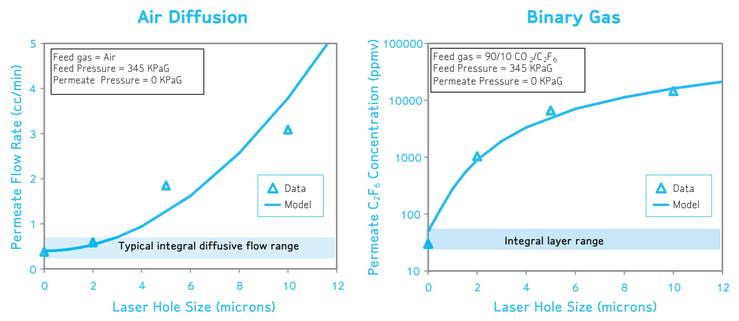
EXPERIMENTAL VERIFICATION

Experimental Verification of Defect Sensitivity

- 142-mm virus membrane discs (127 cm^2)
  - Laser drill holes of 2,5,10 micron sizes
- 0.7 m2 microporous membrane device
  - Insert orifices of 0, 2, 5, 10 micron sizes
- Perform integrity tests
  - Air/water diffusion test
  - 90% CO_2/C_2F_6 binary gas test
- For virus filter, retention test to 75% fouling with IgG and ΘX174

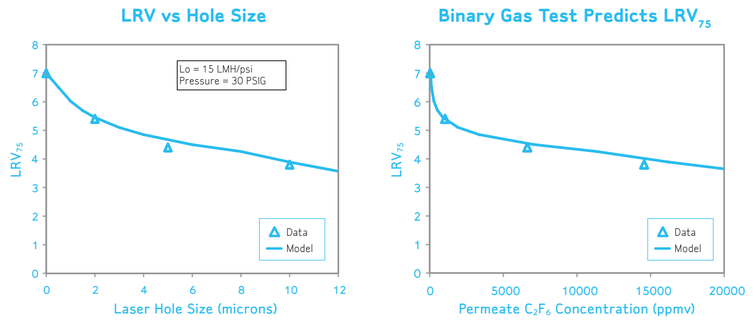


Binary Gas Test Offers Higher LRV Assurance



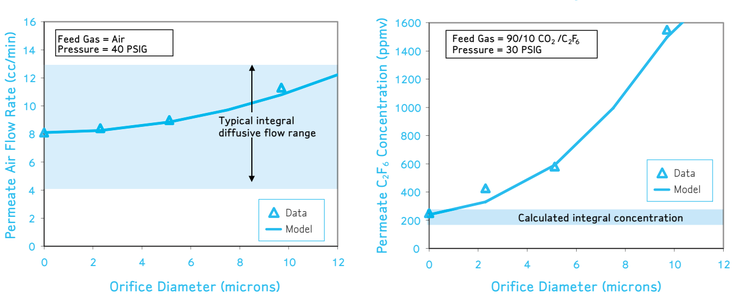
- Data obtained from double layer membrane discs
- Discs drilled with laser holes
- Binary Gas Test far more sensitive to defects than air/water diffusion test

Binary Gas Test Defect Sensitivity – Double Layer Membrane Discs



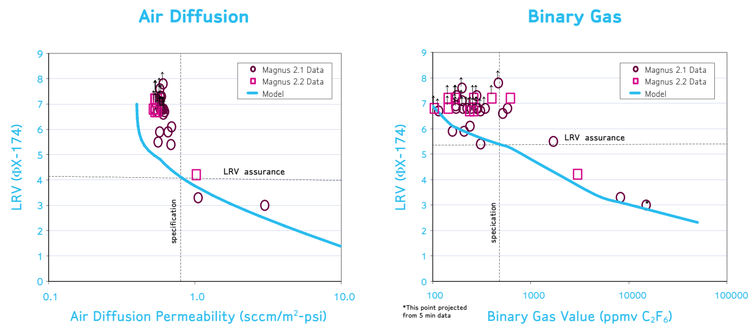
Double layer 142-mm discs of virus filter membrane

Binary Gas Test Offers Higher LRV Assurance



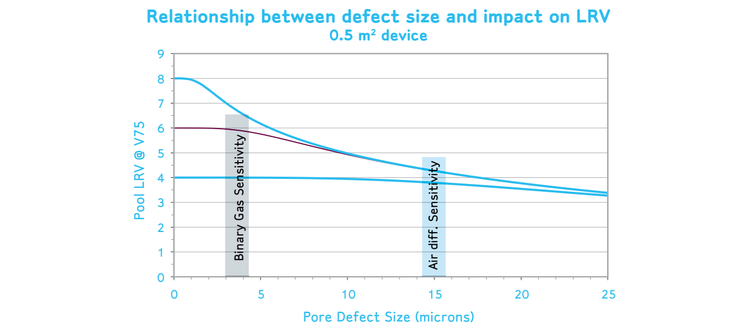
- Data obtained from devices manufactured with various size orifices
- Binary Gas Test detects defects as small as 2-3 microns
- These defects cannot be detected by current technology (air/water diffusion test)

Integrity Testing of Magnus Devices



- Retention data on 24 Magnus 2.1 and 10 Magnus 2.2 devices
  - At least 3 lots of each size
- Defect detection sensitivity of air diffusion and binary gas tests verified
- Binary gas test provides added level of retention assurance

Binary Gas Test Offers Higher LRV Assurance



- Binary Gas Test provides superior sensitivity in detecting small defects that can affect LRV
  - Supported by theoretical and experimental data

TESTING BY MILLIPORE DELIVERS HIGHER LRV ASSURANCE

- **Binary Gas Test is performed by Millipore as part of QC testing**
- **Viresolve Pro devices have been designed specifically to accommodate the Binary Gas Test**
  - Requires sweep gas to maintain constant upstream composition

- Binary Gas Test system dedicated for Viresolve Pro Micro devices

- Multi-function integrity test system dedicated for Viresolve Pro Modus/ Magnus devices
  - Pressure hold
  - Water flux
  - Air diffusion
  - Binary Gas

SUMMARY

- Based on the principle differing gas permeabilities through liquid layer of a wetted membrane
  - Key measurement is gas composition, not gas flow
- Demonstrated superior defect detection sensitivity compared to conventional air diffusion test
- Theoretical model closely predicts measured performance
- Enables the detection of defects in a wide range of device sizes – from <3 cm^2 to > 1.5 m^2
- Used as 100% integrity test for Viresolve Pro devices

Acknowledgements

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