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White Paper

June, 2025

Keywords or phrases:
Sartopore® 2, Average flux, Plugging, Vfinal, SIMCA®

Filter Sizing for Aqueous Pharmaceutical Solutions using Sartopore® 2

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Abstract

Sterilization by filtration is one of the commonly employed technologies in the production of pharmaceuticals and biopharmaceuticals. Most formulations used in the pharmaceutical industry are aqueous in nature, and generally, 0.2 µm-rated filters are used for bioburden reduction or sterile filtration of heat-sensitive products.

The required filtration area is typically determined by small-scale experiments using maximum throughput studies or flow performance.

This white paper compiles the flux, capacity, and plugging of Sartopore® 2 filters for various aqueous solutions with differences in viscosity and composition, and presents a method for determining the area of filter required for filtering the required volume based on flux. SIMCA® was used to analyze data spread and perform the calculation.

Introduction

The filtration of liquids through microfiltration membranes is a widely employed unit operation in the biotechnology and pharmaceutical industries for purification and sterilization. Sterilizing filtration is the process of removing all microorganisms from a fluid stream, without adversely affecting product quality.

Sterilizing filtration is a critical step in ensuring the sterility of liquid drug formulations, particularly injectables and ophthalmic solutions. This method uses membranes with pore sizes of 0.22 µm or smaller to remove bacteria and other microorganisms from the solution.[1] The filters used in sterilizing filtration are validated to ensure that they provide absolute removal of contaminants, making the drug safe for patient use. A comprehensive review of the principles and practice of sterilizing filtration was published.[2] Common applications of sterilizing-grade filters include bioburden and mycoplasma reduction (0.1 µm rated filter) in products prior to terminal sterilization and sterilization of fluids that cannot be terminally sterilized by heat.[3] Direct flow sterilizing filtration (which is sometimes referred to as "dead-end" filtration) is typically operated as a batch operation at constant pressure or constant flow rate.

Typically, filter sizing is performed on scale-down membrane filters to limit product utilization, and then sizing is provided for scale-up batches, with a built-in safety factor (typically 15 – 20% to compensate for various variabilities).

In this white paper, average flux, the maximum throughput (V∞), and plugging of the Sartopore® 2 filter are compared across various aqueous injectable pharmaceutical formulations. These formulations were characterized based on the category of use. The tested solutions differed in their viscosities, pH, and excipient compositions, based on the formulation category and some differences within the same category. The findings are only applicable to aqueous solutions devoid of any suspended particles. The flux for each category of molecule was compared with clean water flux to derive filter sizing for various formulations. The Sartopore® 2 0.2 µm filter — which is comprised of heterogeneous double-layer PES membranes — was used, in combination with a 0.45 µm pre-filter membrane.[4,5]

SIMCA® is a multivariate data analytics software from Sartorius that turns complex data into clear, actionable insights. Used across many pharmaceutical and biopharmaceutical processes, SIMCA® reveals hidden patterns across batches by linking critical quality attributes (CQAs) and other process responses, as well as data from process sensors, spectroscopy, and QC to reveal what truly drives performance. Using machine learning algorithms such as principal component analysis and partial least squares, SIMCA® builds process fingerprints that enable users to compare runs, detect drift early, and quickly pinpoint root causes. SIMCA® is widely used during continuous process development, analysis, and verification to help reduce variability | COGs and to accelerate tech transfer from development to commercial manufacturing scales.

Table 1: Overview of solutions used in this study

Category	Active ingredient	Variable excipients	pH range	Viscosity range [cP]	Strength
Aqueous antibiotics	Mitomycin, Tobramycin, Vancomycin, Lincomycin	Acids, base, WFI, Aromatic alcohol etc.	5.0 – 8.0	1 – 11	40 – 300 mg/mL
Synthetic GnRH antagonist	Ganirelix, Cetroelix	Organic carboxylic acid, Trihydroxy alcohol, diols, WFI	3.0 – 5.0	~ 2	0.25 mg/mL
Benzimidazole	Pantoprazole, Esomeprazole, Rabeprazole, Omeprazole	Sugar Alcohol, base, chelating agents, WFI	10.0 – 11.0	8 – 10	20 – 40 mg/mL
Local Anaesthetics	Lidocaine, Bupivacaine	Salts, Stabilizer, Acid, Base, Chelating agent, salts of acid solution, Preservatives, WFI	6.0 – 7.0	1 – 50	2 – 5 mg/mL
Aqueous anti-cancer injection	Thiotepa, Cisplatin, Bortezomib, Fluorouracil, Gemcitabine, Trabectedin	Acids, base, salts, Sugar alcohol, WFI	4.0 – 7.0	1 – 50	0.05 – 6.00 mg/mL
Buffer | salt solution	Sodium hydroxide, sodium chloride, sodium acetate, tris, Sodium Bicarbonate, Magnesium Sulphate	Salt solutions, WFI	5.0 – 11.0	1 – 2	0.06 – 4.50 M
IV infusion	Mannitol, Dextrose, Sodium chloride	Sugar Alcohols, stabilizers, salt, WFI	3.5 – 7.0	5 – 20	5 – 20%
Ophthalmic solution	Gatifloxacin, Olopatadine, Tafluprost, Brimonidine, Timolol, Phenylephrine Hydrochloride, Diclofenac Sodium, Travoprost	Buffer, chelating agent, surfactant, Trihydroxy alcohol, WFI	6.5 – 7.5	1 – 120	0.004 – 0.500%

Materials and Methods

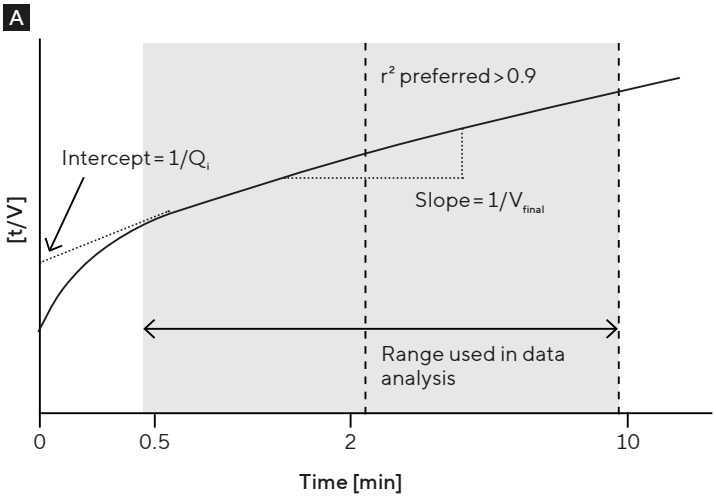
Materials

A Sartopore® 2 (0.45 | 0.2 µm), 47 mm, with 13.5 cm² effective filtration area (EFA), was used for the filtration setup, with Sartorius Zero-T data acquisition and analysis software. Data was collected from different representative feed materials, e.g., aqueous antibiotic solutions, salt solutions, buffers, aqueous ophthalmic solutions, benzimidazole solutions, and local anesthetic solutions. The strength range of each solution is listed in Table 1. Data is further represented and analyzed using SIMCA®.

Methods

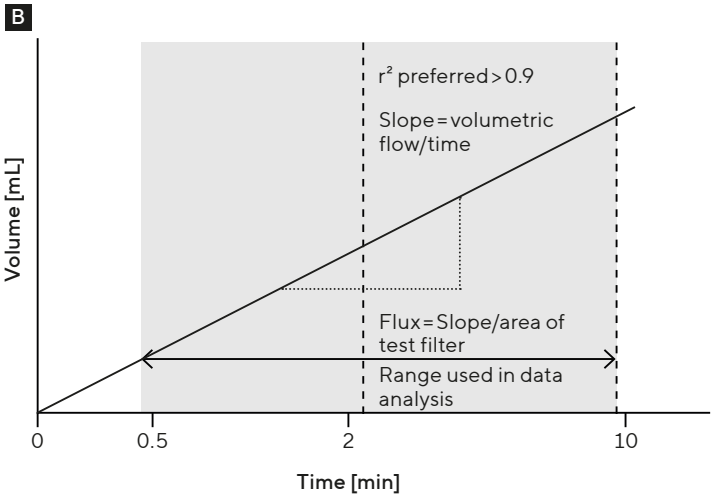
All filtration studies were conducted using a constant pressure of 1.0 bar at ambient temperature. V∞ value, flux, and plugging percentage data for all solutions were derived using a plot of time/volume (t/v) [min/mL] over time [min]. V∞ (V_{final} or V∞) and Qi were obtained experimentally using the plot depicted in Figure 1A. SIMCA® plots were used to represent data sets and analyze the impact of variable solution viscosity on flux data distribution.

Figure 1: (A) Determination of throughput (V_{final} or V∞) from a plot of t/V vs. time. **(B)** Determination of average flux from a plot of volume vs. time



The initial flux (J0) is the inverse of the y-intercept of the regressed line equation divided by the small-scale filter area. V∞ (V_{final}) or filter capacity is the inverse of the slope of the regressed line divided by the small-scale filter area. The slope and y-intercept are easily found using the equation of the line when plotting the t/V vs. t data.

The average flux was calculated from the slope of the volume vs. time graph and divided by the area of the filter (Figure 1B).



A total of 72 data points were considered and analyzed using SIMCA®. Product category, product concentration, and viscosity were considered as variables. V∞, average flux, and filter plugging were considered as outcomes.

Filter plugging by flow was calculated using the initial flux and final flux as follows:

$$\text{Percentage plugging by flow decay} = \frac{[\text{Initial flux} - \text{final flux}]}{(\text{Initial flux})} \times 100$$

The area of the filter required to filter a specific volume at a given time was calculated using the following equation:

$$\text{Required area of filter} = \frac{\left[\dfrac{(\text{Batch volume [L]})}{\text{Average flux [LMH]}}\right]}{(\text{Batch process time [tB]})}$$

The flux through the membrane can be calculated using the Hagen-Poiseuille Equation, which describes liquid flow through cylindrical pores[6]:

$$J = \frac{\varepsilon \times r^4 \times \Delta p}{8 \times n \times \Delta x}$$

where,
J = liquid flux (flow rate through the membrane),
ε = membrane porosity,
r = mean pore radius,
Δp = transmembrane pressure,
n = kinematic liquid viscosity, and
Δx = pore length

Results and Discussion

Filter plugging with respect to the function of flow for the tested solutions is represented in Figure 2 using SIMCA®. The maximum plugging observed on the Sartopore® 2 0.45 | 0.2 µm filter was 19%, while the minimum plugging was 1%.

Flow decay was less than 20%, and the V∞ value for individual solutions was more than 3,000 L/m² (Figure 3). Therefore, all tested feed streams can be considered as non-pore plugging.[7]

Figure 2: Plugging [%] data of individual solutions in the tested product categories

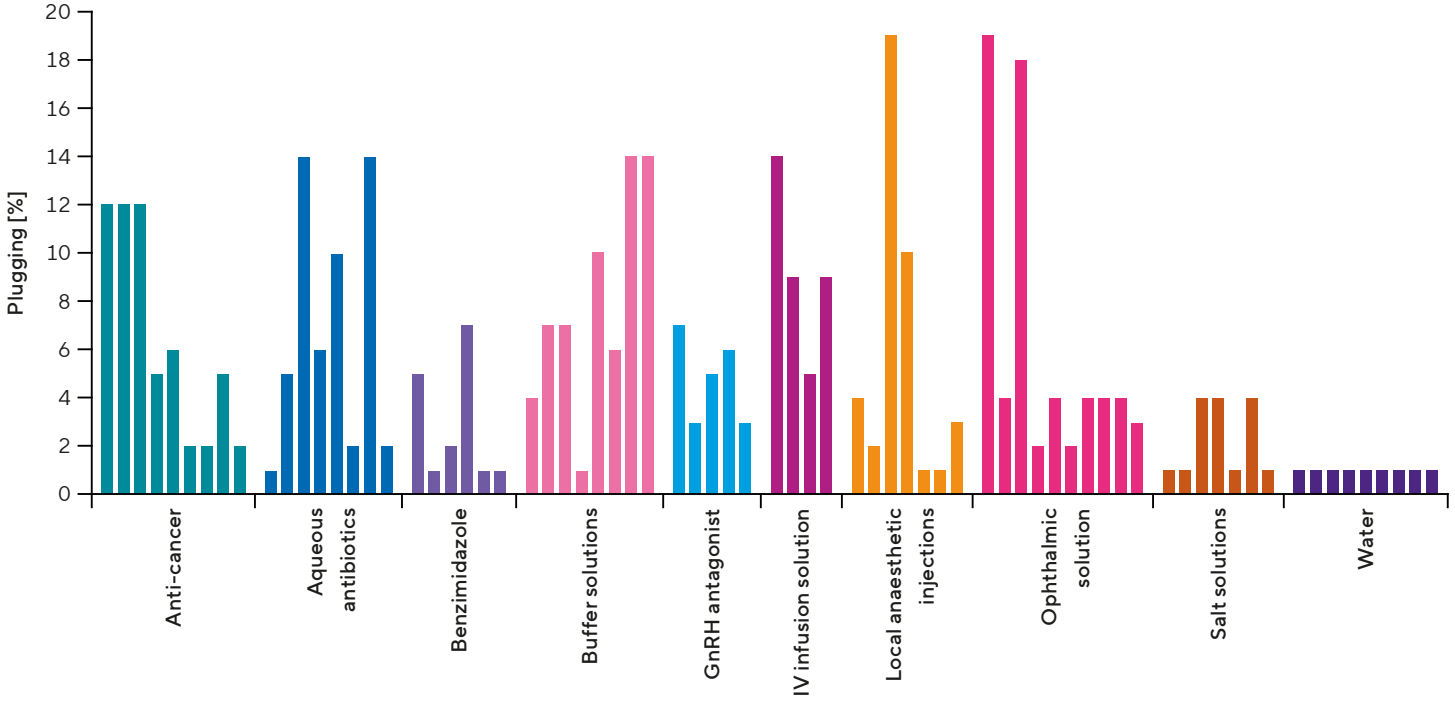
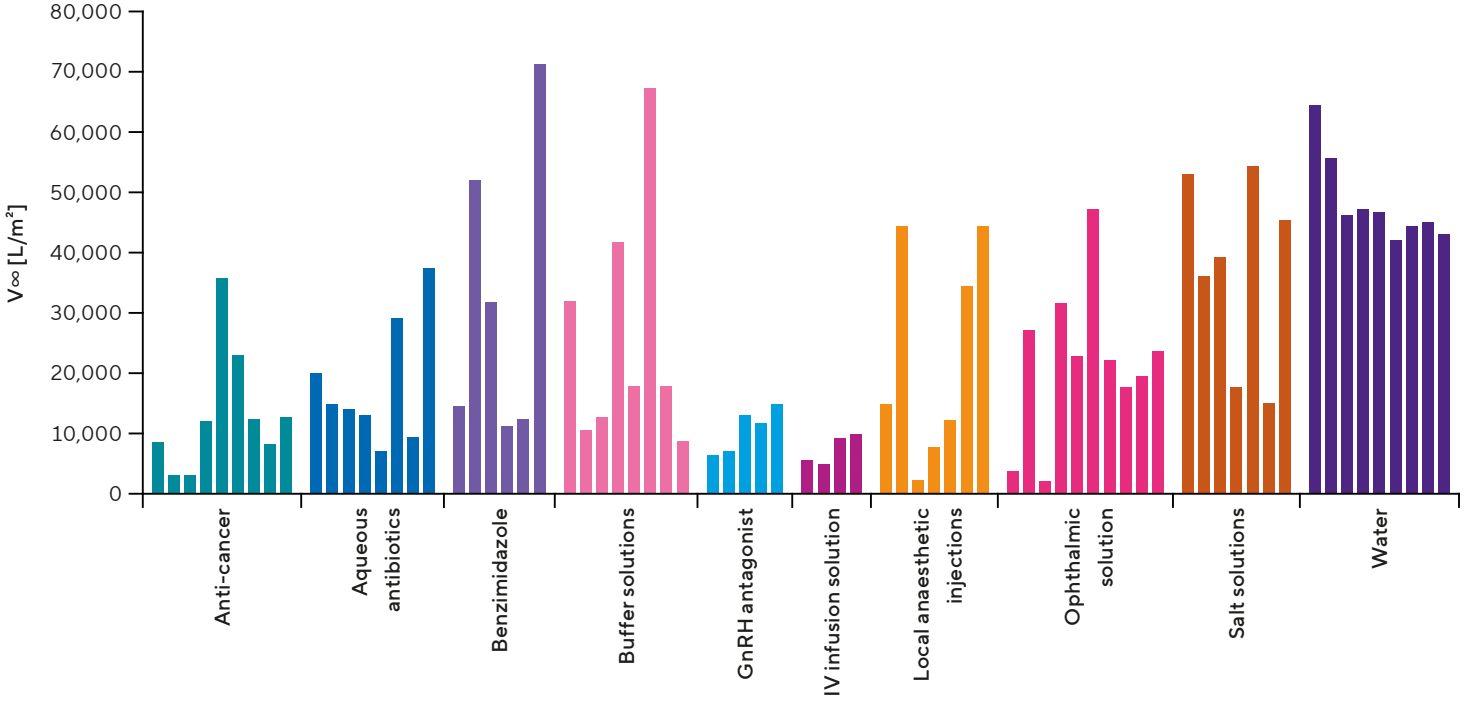
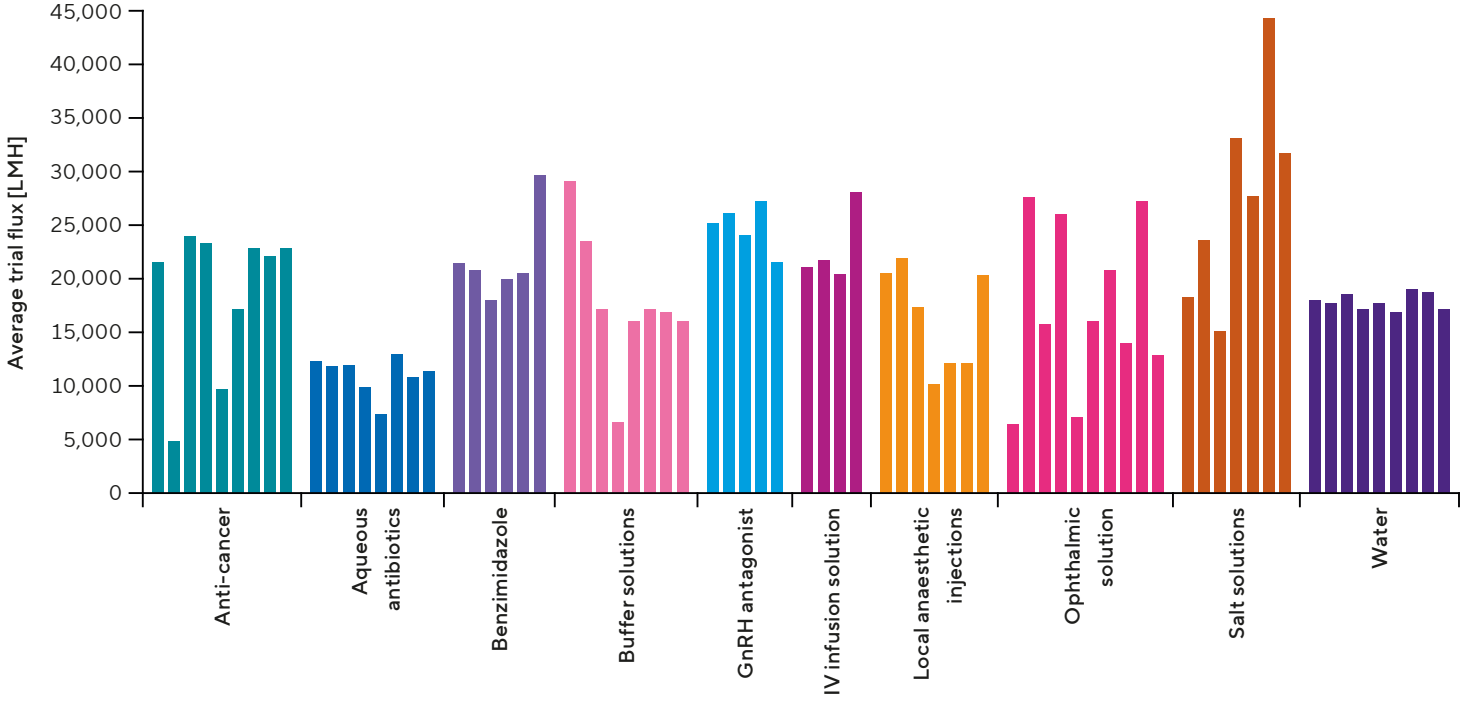


Figure 3: V∞ capacity for individual solutions in the tested product categories



The flux data spread for each tested solution was plotted using SIMCA®, with product category as the x-variable and average flux as the y-variable. The data in Figure 4 represent the spread of flux ranging from > 5,000 LMH to < 45,000 LMH. Each formulation category has some degree of differences in formulation excipients, representing a potential source of variability in flux within them. The impact of pH and salt on nanofilter flux has been previously reported, with salts and high pH increasing membrane permeability.[8]

Figure 4: Flux data for individual solutions in the tested product categories



The data in Figure 5 were statistically analyzed for each category using average flux and applying a confidence interval. The average was calculated based on available experimental data, and then a confidence interval of 90% was applied to derive the maximum and minimum estimated flux value for each category of solution.

The average flux of individual solutions was plotted against viscosity (Figure 6). Four solutions had the same viscosity around 50 cP (green circles, Figure 6), but a variation in flux was observed. This variation could be due to differences in formulation excipients and preparation methods. This indicates that aqueous solutions with similar rheological properties can have variable hydrodynamic properties. Most of the aqueous solutions considered here had a viscosity of less than 20 cP and flux variability from 5,000 LMH to 44,431 LMH. WFI — used as a standard solution with viscosity of 1 cP — had flux in the range of 18,000 LMH.

Figure 5: Estimated flux range for different categories of feed solution

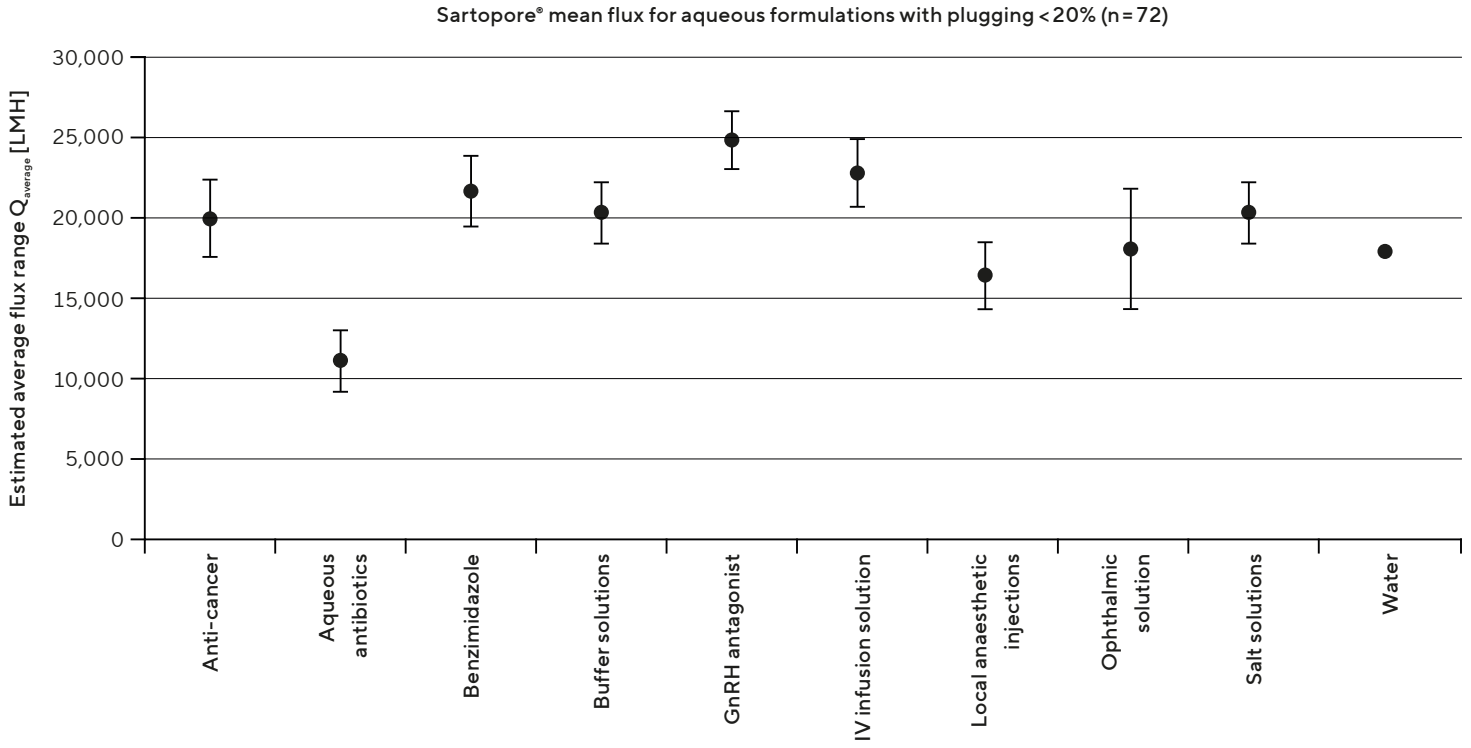
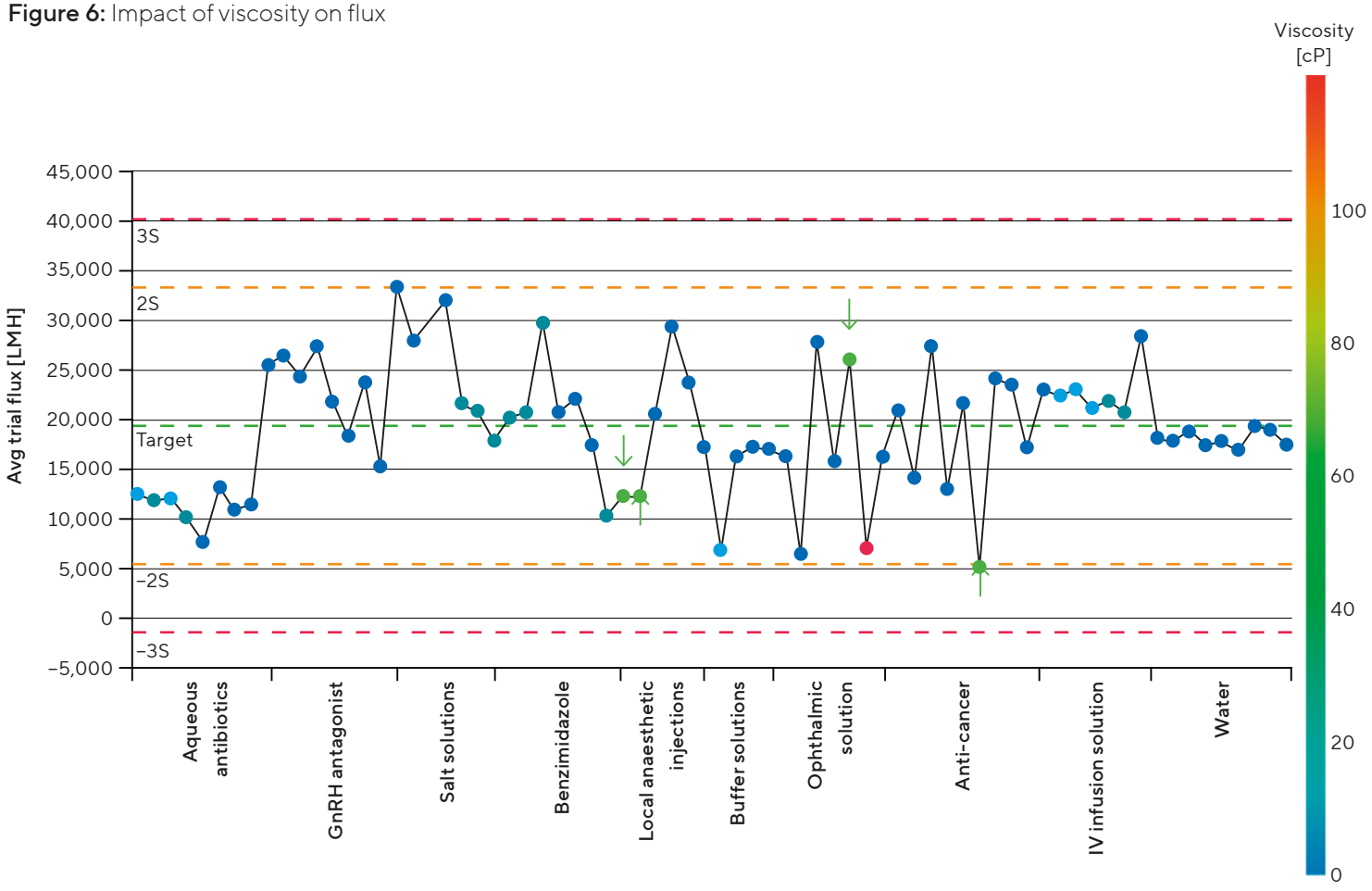


Figure 6: Impact of viscosity on flux



Note. SIMCA® Shewhart control chart showing relation between average flux and viscosity for tested aqueous pharmaceutical solutions

As per the Hagen-Poiseuille Equation, flux through the membrane is directly proportional to the applied differential pressure and inversely proportional to kinematic viscosity of solution.

In this white paper, we observed that there is minimal impact of viscosity up to 20 cP on flux through the Sartopore® 2 membrane. Viscosity started to impact flux at approximately 50 cP and above. The strength of the solution, pH, and the presence or absence of some additives also contributed to variation in flux.

In Figure 6, the observed flux distribution is within two-sigma value (2S) of the mean of approximately 19,235 LMH. The average water flow rate was observed to be 18,084 ± 318 LMH using a 47 mm membrane at 1 bar differential pressure (Figure 5). The variation between the average flow of all tested solutions and the water flow is ~ 6%. The 6% difference in flux may be attributed to random variation in measurement and can therefore be disregarded. Water flow data can be used as a reference for filter sizing for aqueous pharmaceutical solutions with viscosities less than 20 cP.

In commercial manufacturing, flat membranes are not generally employed; typically, pleated membranes are used. Therefore, it would be reasonable to consider the water flow rate of a pleated device, e.g., a cartridge, as a reference standard to derive sizing by applying an appropriate safety factor.

As per the Sartopore® 2 validation guide, the highest achievable flow rate for water with a 30" cartridge is 8,333 LMH at 1 bar differential pressure. The flux ratio between the cartridge and the flat disc membrane is approximately 0.5. Membrane pleating inside the filter cartridge contributes to this variation: Cartridges are more complex in their construction than simple flat discs. The pleating will furnish the added EFA; however, the pleat architecture, the number of pleats and their heights, the nature of the support, and drainage would impact flow dynamics.

Conclusion

SIMCA® can be used to help predict filter sizing requirements for solutions with similar physical and hydrodynamic properties, based on flux. This analysis takes into account various formulation aspects, and it was observed that viscosities below 20 cP and filter plugging up to 19% do not significantly affect the flux. The tested flux was similar to that of water flux, indicating that water flux through the membrane can be used for sizing purposes for non-pore plugging solutions with a viscosity less than 20 cP. Additionally, flow through flat disc membranes differs from that of pleated membranes; therefore, sizing should be based on flux through pleated devices.

As per the Sartopore® 2 validation guide, the highest achievable flow rate for water with a 30" cartridge is 8,333 LMH at 1 bar differential pressure. Thus, 8,333 LMH can be easily used for filter size calculation for aqueous pharmaceutical solutions, and a safety factor of 20% can be applied to the calculated area to compensate for any variation in the process. Table 2 provides indicative sizing for various feed volumes for the Sartopore® 2 filter with respect to process time. These results can be verified using small-scale pleated capsule devices (e.g., capsules of size 4, 150 cm^2) before scaling up.

If the formulation contains any excipients that tend to adsorb on the PES membrane, then adsorption studies must be performed before final filter selection.

Table 2: Sartopore® 2 filter sizing for various feed volumes

Feed	Predicted flux [LMH]	Feed volume [L]	Batch process time (tB [h])	Required area [m^2] Af = (VB/flux)/tB	Required area [m^2] Af = (VB/flux)/tB with 20% Safety	Available capsule area [m^2]	Final flux for capsule [LMH]	Available cartridge area [m^2]
Aqueous pharmaceutical solutions	8,333	2	0.17	0.0014	0.0017	0.015	784	0.3
	8,333	10	0.25	0.0048	0.0058	0.015	2,667	0.3
	8,333	50	0.25	0.0240	0.0288	0.030	6,667	0.3
	8,333	100	0.50	0.0240	0.0288	0.030	6,667	0.3
	8,333	500	1.00	0.0600	0.0720	0.100	5,000	0.3
	8,333	1,000	1.00	0.1200	0.1440	0.200	5,000	0.3

List of Key Abbreviations

Abbreviation	Description
mg/mL	Milligram/mililiter
M	Molar
%	Percentage
V∞	Maximum volume that can pass through the filter
LMH	Liter/square meter/hour
L	Liter
m^2	Square meter
cps | cp	Centipoise
WFI	Water for injection
h	Hour
Af	Area of filter
Vb	Batch volume
tB	Batch process time
inj	Injection
cm^2	Square centimeter

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Last modified: 12 | 2025