

# Application Note

## Eliminating product loss due to preservative binding



### Summary

Preservatives are added to lens care solutions and multidose ophthalmic topical drugs to maintain sterility. A major concern in ophthalmics production is the binding of these preservatives to filtration membranes during processing. This results in product wastage and increased processing costs, especially for blow-fill-seal operations.

Significant variation in preservative binding characteristics in different membranes can mean that the choice of membrane for sterilising ophthalmic products can have a major impact on the economy of the system.

**Parker domnick hunter's unique TETPOR HP filter not only guarantees the sterility of your final product but is also specifically designed to eliminate preservative binding and prevent product loss.**



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#### Key Filtration Requirements:

- **Validated sterilising grade membrane**  
The membrane must be validated to ASTM F838-05 and be correlated to a non destructive integrity test.
- **Low preservative binding**  
Low adsorption of preservatives by the membrane prevents product wastage and increases productivity.

This application note reports the findings of a study into the preservative binding characteristics of Parker domnick hunter's new TETPOR HP membrane compared to PES and PVDF filtration membranes which are in common use for the sterile filtration of ophthalmic preparations and are known adsorb low amounts of preservatives.



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# Introduction

Multi-purpose contact Solutions (MPS) and various topical medications for treatment of chronic ocular diseases such as dry eye and glaucoma are administered in multidose format. These ophthalmic solutions are designed for extended use over a period of weeks and preservatives are a key ingredient to prevent microbial contamination and decomposition of the active drug during this time. Many different types of preservatives are currently used in ophthalmic solutions. Table 1 contains a list of common preservatives with typical concentrations.

Although the industry trend is to move towards reducing the use of preservatives in ophthalmic preparations, especially those intended for extended use, research has shown that preservatives are

necessary in multidose containers to prevent contamination<sup>1, 2</sup> and the cost of producing unit-dose preparations that do not require preservatives is prohibitive. As such, the majority of existing products on the market contain a preservative of some description and are likely to for the foreseeable future.

Two of the most common preservatives found in ophthalmic solutions are Benzalkonium Chloride (BAK) and Polyhexamethylene biguanide (PHMB). BAK has a long history of use and is still the most widely used preservative in ophthalmic solutions today. PHMB has gained recent popularity as manufacturers look to produce ophthalmic preparations free from BAK, which has been linked to ocular surface

damage when used over a long period of time.

Parker domnick hunter has conducted a study into the binding characteristics of different filtration membranes with respect to BAK and PHMB the findings of which are reported here.

Preservative	Synonyms	Typical Concentration
Benzalkonium Chloride	BAK, BAC, BKC, Parasterol	-0.01 %
Polyhexamethylene Biguanide	PHMB, Polyhexanide, Cosmocil®	-0.0001 %
Stabilised Oxychloro Complex	SOC, Purite®	-0.005 %
Polidronium Chloride	Poluquaternium-1, Polyquald®	-0.001 %
Disodium Edetate	EDTA, Edetic Acid, Versine	-0.1 %
Sorbic Acid (Potassium Sorbate)		-0.1 %

Table 1 - List of common preservatives with typical concentrations

## Challenges in Sterile Filtration

Preservatives are used in concentrations in the ppm and ppb range and as such, binding poses particular problems during filtration.

Any adsorption of the preservative onto a filtration membrane can complicate the processing of the solution as the concentration prior to final filling has to be guaranteed and validated. Common methods used during production are:

- Overdosing of the preservative in the region of 120 %.
- Pre-soaking the filter in a high concentration of the preservative so all potential binding sites on the membrane are filled.
- Discarding the filtrate until the required concentration is reached.

Selecting a filtration system to minimise the uptake of preservatives can substantially increase the throughput of the sterile filtration line and simplify the production process, especially on MPS solutions that may be produced in batches of 10,000 litres.

Low preservative binding during sterile filtration on blow-fill-seal machines is of vital importance as discarding below specification packaged product is even more costly.

## Variation in Membrane Binding Characteristics

The variation in preservative adsorption characteristics of different polymer membranes can be significant.

The surface chemistry of a filtration membrane can have a significant impact on its preservative binding properties and therefore, preservative adsorption can vary from one membrane to another. Parker domnick hunter commissioned an independent study in 2007 into the relative binding characteristics of four various

sterilising grade membrane materials on the market at that time – polyethersulfone (PES), polyvinylidene fluoride (PVDF), cellulose nitrate and nylon.

A commercially available eyewash containing the preservative benzalkonium chloride (BAK) in a concentration of

0.01 % weight / volume was used for the study. BAK was chosen as the preservative as it is still the most widely used preservative in ophthalmic preparations and the assays for detection are the simplest to develop leading to more accurate measurements.

The results represented in figure 1 show the relative volume of the ophthalmic solution that was processed before the concentration of BAK in the filtrate reached 95 % of the original concentration; this is typically the point at which the filling operation can begin.

A huge variation in BAK binding characteristics were seen from the highest (nylon) to the lowest (PES).

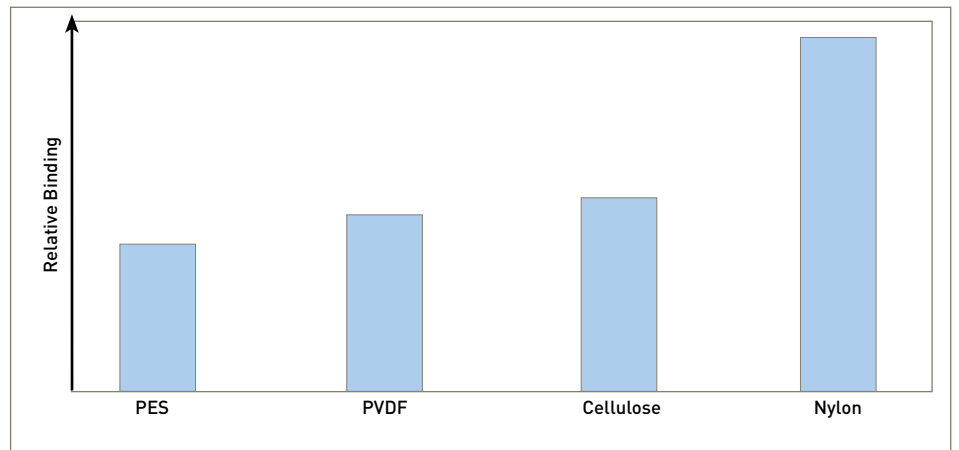


Figure 1 - Relative binding of different filtration membranes for benzalkonium chloride (BAK)

## Evaluation of New Filtration Membrane

Parker domnick hunter's TETPOR HP has been specifically designed to eliminate preservative binding during sterile filtration.

As the lowest preservative binding membrane on the market at the time, PES was chosen as a comparison in the evaluation of the TETPOR HP during its development. A PVDF membrane was also tested.

A study into the preservative binding properties of the three membranes was conducted using membrane discs on a solution of BAK at a concentration of 0.001% weight / volume BAK. The concentration of BAK in the filtrate was measured at regular time intervals for 5 minutes for each membrane using UV spectrometry. The results in figure 2 show the rate of recovery of the filtrate to 95% of the original concentration.

It can be seen that the initial filtrate from the TETPOR HP contains 98% of the original BAK concentration. This means that the filling operation could begin immediately with no filter preconditioning or product wastage.

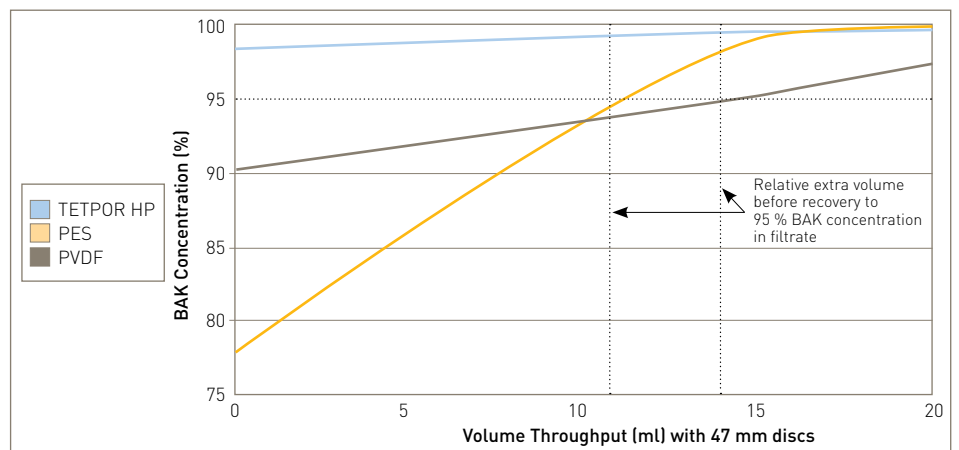


Figure 2 - Preservative binding characteristics of TETPOR HP against PES and PVDF membranes on 0.001 % BAK

The PES membrane showed low preservative binding but some processing was required to reach 95% BAK concentration in the filtrate. PVDF required further processing of the BAK solution to reach the target level. Processing with PES or PVDF filters would require the use of a validated method to

guarantee the BAK concentration in the final product.

Similar results have also been seen for the TETPOR HP using PHMB, another common preservative used in ophthalmic preparations.

# Conclusion

This study has shown that the hydrophilic PTFE membrane incorporated in TETPOR HP filter cartridges adsorbs much lower levels of benzalkonium chloride, a common ophthalmic preservative, than PES and PVDF membranes, which are known to exhibit low binding characteristics. Using the TETPOR HP for the sterile filtration of ophthalmic solutions can have significant cost benefits by:

- Removing the need for filter preconditioning saving time and simplifying the production process.
- Reducing or eliminating product wastage from discarding out-of-spec final product due to preservative binding.
- Preventing or eliminating product from blow-fill-seal operations from being rejected.

## References

- <sup>1</sup> Schein OD, Hibberd PL, Starck T, Baker AS, Kenyon KR. Microbial contamination of in-use ocular medications. *Arch Ophthalmol* 1992;110:82-85.
- <sup>2</sup> M Q Rahman, D Tejwani, J A Wilson, I Butcher, and K Ramaesh, Microbial contamination of preservative free eye drops in multiple application containers, *Br J Ophthalmol*. 2006; 90(2): 139-141

# Product Selection

The right product for your application

Product	Membrane	Main Feature	Cost Saving Benefit
TETPOR HP	Hydrophilic PTFE	Zero binding of preservatives	Filling can begin immediately without preconditioning of filters to eliminate product wastage.
PROPOR SG	PES	Very high flow rates	Faster processing for minimal batch turnaround time.
PROPOR HC	PES plus PES prefilter layer	Increased capacity	Economical filtration of difficult to filter solutions with a high concentration of viscosity enhancer.

N.B. This table is for guidance only. Filterability can vary from one solution to the next and Parker domnick hunter recommends that filterability studies are conducted on an individual basis to ascertain the optimal filtration system.

# Products

## Sterile Liquid Filtration

### PROPOR SG

0.2 micron

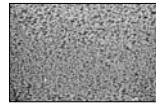


Polyethersulphone

- High flow
- Low preservative binding

### PROPOR HC

0.2 micron

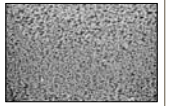


Polyethersulphone

- High capacity
- Low preservative binding

### PROPOR LR

0.1 micron

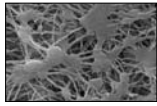


Polyethersulphone

- Retentive to diminutive organisms
- High flow rates

### TETPOR HP

0.2 micron



Hydrophilic PTFE

- Elimination of preservative binding

### PORECHECK IV

Integrity Testing



- Bubble point testing
- Diffusional flow / pressure decay testing
- Water intrusion testing

## Liquid Filtration

### PROPOR BR

0.2 micron

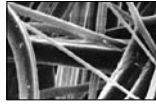


Polyethersulphone

- Bioburden reduction
- Maximum throughput

### PROCLEAR PP

0.6 - 100 micron

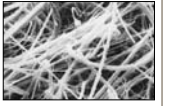


Polypropylene

- Particulate removal
- Robust to withstand aggressive chemicals

### PROCLEAR GF

0.6 - 10 micron

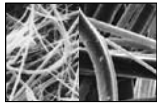


Glass Fibre

- High capacity
- Maximum throughput

### PROCLEAR GP

0.5 micron



Glass Fibre / Polypropylene

- High capacity
- Maximum protection of downstream membrane

### Housings

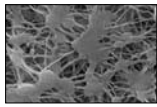


- A full range of stainless steel housings specifically designed for pharmaceutical applications

## Sterile Gas Filtration

### TETPOR AIR

0.2 micron

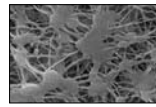


PTFE

- Validated by liquid and aerosol challenge

### HIGH FLOW TETPOR II

0.2 micron

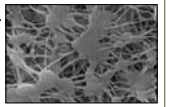


PTFE

- Unrivalled flow rates
- Validated by liquid and aerosol challenge

### HIGH FLOW TETPOR HT

0.2 micron

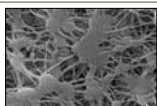


PTFE

- Continuous use at high temperatures
- Validated by liquid and aerosol challenge

### TETPOR PLUS

0.2 micron



PTFE

- Resistant to chemical attack
- Ideal for venting of ozonated water tanks

### VALAIRDATA II

Integrity Testing



- Aerosol challenge testing
- Integrity testing of gas filters

### Housings



- A full range of stainless steel housings specifically designed for pharmaceutical applications

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