Summary
Viscosity enhancers are key ingredients in many lens care solutions and ophthalmic prescriptive drug products. These additives are commonly cellulose based compounds but hyaluronic acid is becoming increasingly popular in new formulations.

Solutions containing viscosity enhancers can present difficulties during sterile filtration due to batch to batch variability. Even with careful optimisation of the mixing process, premature filter blockage is still common resulting in frequent filter changeouts mid-batch, product loss and increased processing time.

Parker domnick hunter’s PROPOR HC has been specifically designed for difficult to filter solutions so we can provide sterile filtration systems that deliver the fastest and most cost-effective batch processing available.

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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.

- **Maximum throughput**
  The sterile filtration system must be able to process ophthalmic solutions containing cellulose based or other viscosity enhancing ingredients without blockage whilst minimizing system size.

- **High flow rates**
  A fast flowing filtration system will minimize processing times decreasing batch turn around time.

This application note highlights an example of Parker domnick hunter’s experience in designing filtration systems for cellulose based ophthalmic solutions. Working with a large global manufacturer on the optimization of their production line for a dry eye treatment, we were able to reduce the system size by 25% whilst slashing processing time by 75%.
Introduction

Manufacturers of ophthalmic products are constantly looking to develop innovative new multipurpose solutions for contact lens users and prescriptive drugs for treatment of eye conditions. One of their main aims is to increase the residence time of ophthalmic solutions in the eye, adding to user comfort when using contact lens products and increasing the efficacy of delivery of the active pharmaceutical ingredient (API) in prescription drugs. This has driven the use of viscosity enhancers such as cellulose based additives and, more recently, hyaluronic acid.

Common cellulose based additives used in existing ophthalmic products on the market today include carboxymethylcellulose (CMC), hydroxyethylcellulose (HEC) and hydroxypropylmethylcellulose (HPMC). These viscosity enhancing ingredients can pose challenges for sterile filtration.

Parker domnick hunter recently had the opportunity to work with a large global ophthalmic manufacturer on the optimisation of the production line for a particularly difficult to filter solution for the treatment of dry eye, which contains CMC.

During the optimization process it became evident that the filtration train was just one of the factors influencing the volume throughputs which could be achieved. There are a number of processing parameters which may also contribute and it is hoped that by highlighting these issues, other manufacturers will be able to take them into account when implementing their own process improvement initiatives.

The Problem

Multiple filter changeouts during batch processing

The production line for the ophthalmic solution in question was targeted as part of an ongoing process improvement at the manufacturer’s site to increase production yield by 80 per cent. Even after extensive optimization of other parts of the production process not related to the filtration train and careful mixing of the solution in a high shear mixer, premature filter blockage in the existing filtration train still occurred. This resulted in extended processing times, product wastage and indirect costs due to non-compliance of the process when filter changeouts were necessary mid-batch.

The existing filtration train consisted of three stages as shown. To process the full 1000 L batch, the first two filtration stages frequently required up to two or three changeouts mid-batch resulting in processing times of up to 8 hours with a significant volume of product loss.

Focusing on the first two filtration stages, the current filtration supplier and three others, including Parker domnick hunter, were invited by the manufacturer to investigate and propose a filtration train with the ultimate objective of being able to guarantee full batch processing of the difficult to filter solution.
Batch-to-Batch Variability

The influence of raw materials and process parameters

During Parker domnick hunter’s initial filterability testing, it became apparent that there was large batch-to-batch variability in the filterability of the manufacturer’s solution. This can be due to a number of factors.

- CMC or other cellulose based viscosity enhancers are often more widely used in industries such as the food industry where specifications are not as strict. Granularity of the raw CMC is one of the key measurements required to minimize batch to batch variation and its effect on filterability.

- Mixing techniques can also influence a filter’s performance. The hot / cold technique is often used with cellulose viscosity enhancers. The cellulose is dispersed and thoroughly mixed at high temperature at which point the cellulose is insoluble. This is followed by rapid cooling to a point where the cellulose becomes water soluable. If this is not controlled well premature blinding of filters can quickly occur.

- The temperature of the solution is also of importance during the filtration process. Increasing the temperature can promote gelation of the solution that will lead to premature blinding of a filter. The heat generated on a pumped system can have significant impact of the volume that can be processed through the filter and lead to sudden blockage during the processing of a batch.

- The filterability of solutions can change significantly depending on the time between mixing and filtration. Graph 1 shows an example of this variation, encountered by Parker domnick hunter during filterability studies on a 0.5% HPMC solution.

When designing the filtration system, a supplier must have an understanding of all of the variables that may affect the filterability of the solution. Ideally, if new systems are proposed, they should be tested concurrently with the existing filter train to eliminate any variability in the preparation of the solution.

Graph 1 - The influence of batch quality and age of solution on filterability of an ophthalmic solution containing 0.5% hydroxypropyl methylcellulose (HPMC)
Optimizing the Filtration System

Competitive filtration solutions

The existing filtration supplier and three others, including Parker domnick hunter, proposed their optimal filtration trains for stages 1 and 2 for the CMC containing solution difficult to process. The filter systems proposed were based on lab-scale filterability studies and full-scale on-site trials. The filtration systems put forward are shown in Table 1.

The Parker domnick hunter filtration system reduced stages 1 and 2 of the original filter train down to a single stage. The PROPOR HC is a dual layer sterilizing grade polyethersulphone (PES) product, incorporating a highly asymmetric integral PES prefilter layer upstream to a sterilizing grade PES membrane. The PROPOR HC is designed to maximize throughput for difficult to filter solutions.

Graph 2 illustrates the size of the Parker domnick hunter system proposal compared to the other filtration suppliers’ systems.

In addition to reducing the size of the filtration train and removing stage one, the Parker domnick hunter system processed the entire 1000 L batch of the ophthalmic product in only 21 minutes. This was a dramatic improvement over the existing system, where times of up to 8 hours had been observed.

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing supplier</td>
<td>40¨ 0.2 µm mixed</td>
<td>0.2 µm PVDF</td>
<td>Not tested.</td>
</tr>
<tr>
<td></td>
<td>Cellulose Ester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplier A</td>
<td>20¨ 0.2 µm PES</td>
<td>20¨ 0.2 µm PES / PVDF</td>
<td>Flow rate significantly reduced after 15 mins.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Batch processing time in excess of 2 hrs.</td>
</tr>
<tr>
<td>Supplier B</td>
<td>3 x 20¨ 0.45 µm</td>
<td>3 x 20¨ 0.2 µm</td>
<td>System size too large.</td>
</tr>
<tr>
<td></td>
<td>Cellulose Nitrate</td>
<td>Cellulose Nitrate</td>
<td></td>
</tr>
<tr>
<td>Parker domnick hunter</td>
<td>Eliminated</td>
<td>2 x 20¨ 0.2 µm</td>
<td>Elimination of filter changeouts.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PROPOR HC PES</td>
<td>Batch process in 21 mins.</td>
</tr>
</tbody>
</table>

Table 1 - Various filtration systems proposed

Graph 2 - Overview of proposed system from filtration suppliers

SEM of upstream side

SEM of upstream side

Cross section showing highly asymmetric structure
Conclusion

By working closely with the product manufacturer, Parker domnick hunter has gained a thorough understanding of the production process and factors affecting the filterability of difficult to filter ophthalmic solutions containing cellulose based viscosity enhancers. For the CMC containing solution investigated, Parker domnick hunter’s PROPOR HC product has provided significant improvements by:

- guaranteeing full batch processing
- reducing system size
- eliminating one filtration stage
- shrinking processing times

Product Selection

The right product for your application

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

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

### 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

**TETPOR PLUS**
- 0.2 micron
- PTFE
- Resistant to chemical attack
- Ideal for venting of ozonated water tanks

**HIGH FLOW TETPOR HT**
- 0.2 micron
- PTFE
- Continuous use at high temperatures
- Validated by liquid and aerosol challenge

**VALAIR DATA II**
- Integrity Testing
- Aerosol challenge testing
- Integrity testing of gas filters

### Housings

**TETPOR HP**
- Hydrophilic PTFE
- Integrity Testing
- Housings
- A full range of stainless steel housings specifically designed for pharmaceutical applications