

The Effects of Exposure Conditions on the Level of Filter Extractables/Leachables



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Purpose of Study

Extractables and leachables are addressed as a part of a material validation program. Disposable, single-use, plastic materials are commonly used throughout the pharmaceutical process. While extractables and leachables should be addressed for all processing materials, it is particularly important that they be addressed for the final sterile filters due to their proximity to the final fill. While polymeric sterile filters may be small in size, they have a contact surface area in great excess of the filtration area due to the porous structure of the filter material.

Processing conditions can have an effect on the level of filter leachables that actually migrate into a drug formulation. Ideally, these process conditions are modeled during the leachable study. This study was performed to better define the significance of processing conditions on leachable compounds. Understanding the general effects of the various conditions will aid in the choice of the best test parameters for a leachable study with the actual drug formulation at simulated process conditions



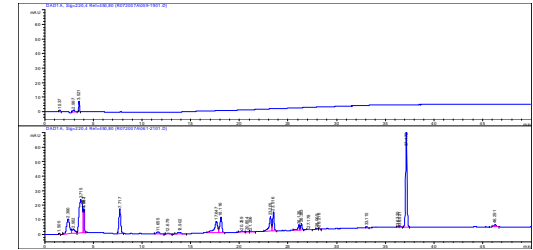
Experimental Design

Sterilizing grade polyethersulfone (PES) filters were extracted at various processing conditions. Process conditions investigated included: exposure time, exposure temperature, sterilization method (autoclave, gamma irradiation), and rinsing as a pretreatment step. The extraction technique (static, shaken, and recirculation) and two extraction solvents were also investigated. The sample controls and extraction samples were analyzed using RP-HPLC (Reverse Phase High Performance Liquid Chromatography) with a gradient method using acetonitrile and water.

Conditions

❖ Solvent

Isopropyl Alcohol (IPA) vs. Water



- IPA Extracted Greater Number of Extractables

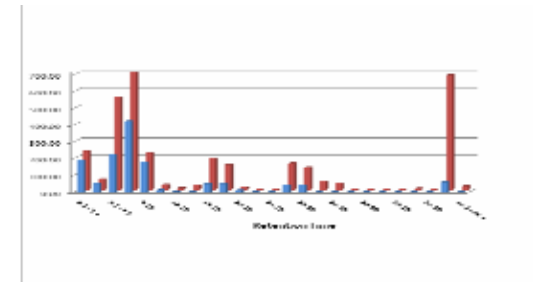
❖ Exposure Time

IPA at 50 °C Time Points

- Extractable Compounds Extracted at Different Rates
- Extractables Reached Maximum Abundance at Various Time Points

❖ Temperature

Room Temperature (RT) vs. Elevated Temperature (50 °C)



- Each Extractable Compound Detected at Both Temperatures
- Elevated Temperature Caused an Increase in the Peak Area (Quantity) of Each Extractable

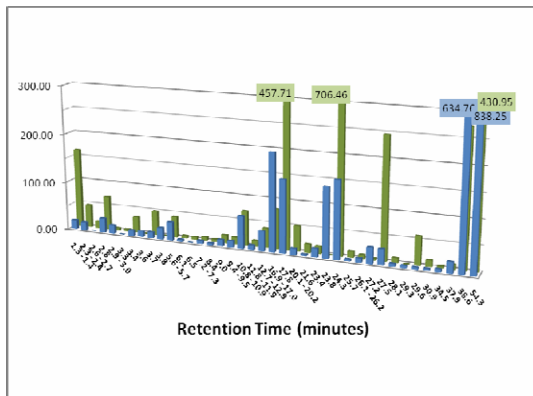
❖ **Sterilization**

Autoclave vs. Gamma Irradiation vs. Control (No Sterilization)

- Different Sterilization Methods Caused Unique Extractable Profiles
- Sterilization Caused a General Increase of Extractable Levels

❖ **Rinse**

Rinse using 4 L of Water for Injection (WFI) vs. Control (No Rinse)



- Different Rinse Methods Caused Unique Extractables Profiles
- Water Not an Effective Rinse for Solutions Containing substantial Organic Compounds

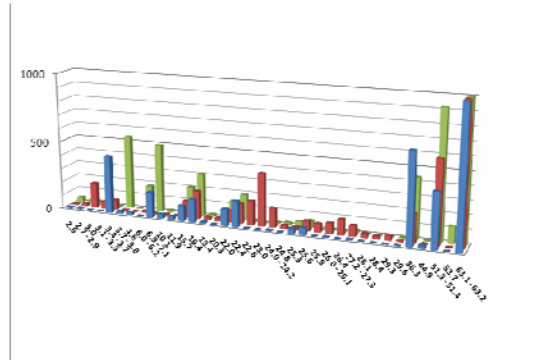
❖ **Extraction Test Technique**

Static vs. Dynamic vs. Recirculation Extraction of Filter with IPA (50 °C)

- Shaking the Test Filter Promotes Solvent Contact with All Filter Surfaces
- Shaking Eliminates the Formation of Concentration Gradients
- Recirculation Requires Greater Solvent Volume which Dilutes Extractable Compounds
- Recirculation Introduces Tubing which Can Contribute Extractables

❖ **Filter Manufacturer**

Polyethersulfone (PES) Capsules from Three Manufacturers IPA Extraction at 50 °C



- Extractables Profile Unique Even Though Same Filter Membrane Materials
- Possible Sources of Differences are Resin Additives, Processing Aids, etc.

Conclusions/ Recommendations

- When designing and performing leachable testing it is important to mimic process conditions.
- Process time should be reproduced during testing since leachable levels vary with time.
- Leachables test should be performed at a temperature that targets the high range of the process temperature to ensure detection of maximum quantity of leachables.
- Filter pretreatment steps (sterilization, rinse) have unique effects on leachables and should be reproduced during testing.
- Shaking the filter is an adequate extraction technique.
- Filters from different manufacturers may produce unique leachables results.
- Chemistry of product formulation effects the types of leachables extracted. Ideally, the actual product formulation should be used during leachables testing.

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