

Overview

Fluoropolymer (PFA and FEP) bottles are widely used in the pharmaceutical industry process stream for the storage and transfer of pharmaceutical intermediates including API (active pharmaceutical ingredient). They are also used for the bulk storage of temperature sensitive products such as vaccines. Fluoropolymers are ideally suited to these types of applications due to their chemical inertness, wide working temperature range (-200°C to 260°C) and cleanliness. The unique design features of Purillex™ PFA and FEP bottles, manufactured by Saville, makes them the best choice for use in the biopharmaceutical industry. Purillex bottles are the only fluoropolymer bottles manufactured using stretch blow molding technology, which offers significant benefits for transfer and long term storage of valuable biopharmaceutical products.

The wide mouthed GL45 closure is a standard in the pharmaceutical industry and the superior sealing ability of the neck and closure ensures unmatched preservation of content integrity. Purillex bottles are non-cytotoxic, USP Class VI compliant, and manufactured in a clean room from the highest purity grades of virgin PFA and FEP resin, ensuring the highest levels of cleanliness.

In order to support end user product-contact evaluations for biopharmaceutical applications, Purillex bottles were subjected to extensive third party testing for organic and inorganic extractables. Both 7-day and 28-day extraction tests using multiple solvents at elevated temperatures were carried out. This technical note summarizes the test results, along with the methodology and instrumentation used. Complete reports^{1,2}, with all analytical methodology and data for both Purillex PFA and FEP bottles are available on request from Saville.

Extractables Testing – Scope

Measuring the type and amount of organic and inorganic compounds extracted from the surface of any material that comes into contact with a biopharmaceutical product is critical to validating it for use, since it directly impacts the safety, quality and purity of the product. Extractables testing (also referred to as forced extraction testing) employs test protocols that use aggressive extraction solutions and elevated temperatures, to simulate worst-case scenarios and is carried out by pharmaceutical companies to evaluate product-contact materials.

Extract Collection Procedure

All testing was performed by the DuPont Corporate Center for Analytical Sciences, Wilmington, DE, USA.

In order to thoroughly test the Purillex bottles, a range of extraction solutions, including more aggressive extraction solutions than those typically used, were selected and are listed below:

- DDIW (ultrapure distilled deionized water)
- pH3 acidic buffer solution (citrate buffer)
- pH10 alkaline buffer solution (carbonate buffer)
- Polar organic solvent (methanol)
- Non-polar organic solvent (n-hexane)



Purillex™ 2000 mL Bottle

Two different types of Purillex bottle were tested: 250 mL PFA and 250 mL FEP. Six samples of each type were tested for each of the five extraction solutions. All bottles were manufactured using high purity grades of DuPont™ Teflon® PFA and FEP resin. The bottles were autoclaved at 121°C for 75-90 minutes, allowed to cool and rinsed with DDIW prior to use.

One challenge with the use of complex extraction solutions is sourcing clean starting materials. The pH3 buffer was prepared using ACS grade anhydrous citric acid to create a 0.1 M citric acid solution. The pH10 buffer was prepared using ACS grade sodium carbonate and Sodium bicarbonate salts to create a 0.1 M carbonate solution. The methanol used for the extraction studies was semiconductor grade. The hexane used was HPLC grade. Despite the use of highest available purity reagents, blank contamination was an issue for some tests, as will be described later.

The bottles were filled with 250 mL of the extraction solutions and the Purillex closure fitted and tightened. As with all Purillex bottles, no closure liner or seal is required. The bottles containing DDIW were kept at 70°C while the remaining extraction solutions were kept at 35°C. Of the six bottles filled with each of the extraction solutions, three bottles were sampled after seven days and the remaining three bottles were sampled after 28 days. The surface contact area of the bottles (total extractable area) was calculated to be 160.96 cm² (0.0161 m²).

Instrumentation and Analytes

The extracts were measured using the following techniques and instrumentation:

Organic Techniques

- HPLC (UV detection) – Agilent 1100 Series
- LC/MS - Agilent 1100 Series MSD
- GC - Agilent 7890A Series
- GC-FID - Agilent 7890A Series/6850 FID
- GC-MS - Agilent 7890A Series/5975C MSD
- Total organic carbon – Analytik Jena multi N/C 2100S TOC analyzer
- Conductivity – conductivity meter

Organic Analytes

- HPLC/UV/MS - four different methods were used to cover the widest possible range of compounds – APCI and ESI used in both positive and negative modes
- GC-FID, GC/MS - direct and headspace analysis for semivolatiles and volatiles
- TOC analyzer - inorganic carbon (IC) subtracted from total carbon to give TOC. IC was measured following a phosphoric acid digestion.

Inorganic Techniques

- ICP-MS – Thermo Element2 HR-ICP-MS (DDIW samples)
- ICP-MS – Agilent 7500ce ICP-QMS (pH3 and pH10 samples)
- ICP-MS – Agilent 7700x ICP-QMS (methanol and hexane samples)

Inorganic Analytes

In accordance with the requirements of methods currently being developed for the measurement of elemental impurities in pharmaceutical products, all analytes listed in USP Chapter 232 and ICH Guideline Q3D Classes 1, 2A, 2B and 3 were measured. The analyte list is:

Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Ti, V

Note:

- Mn was also analyzed but has been removed from the USP Chapter 232 analyte list
- The samples were measured using a combination of ICP-MS instrumentation as described above
- Full method details for both organic and inorganic analytes can be found in the complete reports^{1,2}, available from Savillex on request

Results

Organic Analytes

HPLC/UV/MS - no detectable non-volatile compounds were found (no observable difference between blank and sample) in any of the extraction solutions, for both 7-day and 28-day extracts, and for both PFA and FEP.

GC-FID, GC/MS - no detectable semivolatile or volatile compounds were found (no observable difference between blank and sample) in any of the extraction solutions, for both 7-day and 28-day extracts, and for both PFA and FEP.

Chromatograms generated for each measurement are shown in the complete reports^{1,2}.

TOC Analyzer - no detectable TOC levels were found (no observable difference between blank and sample) in the DDIW, for both 7-day and 28-day extracts, and for both PFA and FEP. The other extraction solutions were not measured due to the fact that high levels of carbon were present in the blank solutions. Detection limit and quantitation limit for TOC were 0.48 and 1.69 mg/L respectively.

Conductivity - conductivity changes could potentially indicate the extraction of compounds unidentified by other techniques. No significant change in conductivity was detected over 28 days.

Inorganic Analytes

Of all trace metals analysis techniques in common use, ICP-MS (especially HR-ICP-MS) is by far the most sensitive. While pharmaceutical analysis for trace metals has been typically performed by ICP-OES, it was decided to use the much more sensitive technique of ICP-MS. Full quantitative analysis (method of standard additions) was used throughout. Semiquantitative analysis, though faster, is only accurate to +/-30% at best, and so was not used. Due to the very high sensitivity of ICP-MS, it is very difficult to obtain very low blanks with organic or complex inorganic extraction solutions – even though ACS and semiconductor grade reagents were used. For this reason, hexane extract data was not reported since the hexane (HPLC grade) contained inorganic impurities, and the analysis of the hexane extract was indistinguishable from the blank.

Ultratrace levels of some metals were detected in some of the other sample extracts. The highest total levels were found in the pH3 buffer, as expected, due to its strong extraction power for metals. Even so, the total weight of all measured analytes extracted from each bottle by the pH3 buffer was less than 0.0125 ug (12.5 ng) - an extremely small amount. The other solutions extracted less than 0.0063 ug (6.3 ng). Expressed as analyte weight found per square meter of contact area with the bottle surface, all extracts were found to contain less than 1 ug/m² (total of all analytes measured).

Analyte concentrations were not significantly different in the PFA bottle extractions compared to the FEP bottle extractions, although the methanol extract in PFA had slightly lower analyte concentrations than in FEP. No significant concentration increase was observed in the 28-day extracts compared to the 7-day extracts.

A summary of the inorganic results is shown below. The complete reports^{1,2} express analyte concentration in the extract solution, on a per analyte basis, in ug/m³. For convenience, the table below gives a total concentration (sum of all inorganic analytes) in ug/m³ for each solvent and bottle type. This is also expressed as total weight (ug) of inorganic analytes (sum of all inorganic analytes) extracted from each 250 mL bottle. Finally, this total weight of inorganic analytes extracted is expressed as weight per contact area (ug/m²), using a value of 0.0161 m² for the contact surface area of a 250 mL bottle.

Extract Solution	Bottle Type	Concentration Found (sum of all inorganic analytes)	Total Weight Found Per 250 mL Bottle (sum of all inorganic analytes)	Weight Found Per Contact Area (sum of all inorganic analytes)
DDIW	PFA	<25 ug/m ³	<0.0063 ug	<0.39 ug/m ²
DDIW	FEP	<25 ug/m ³	<0.0063 ug	<0.39 ug/m ²
Methanol	PFA	<10 ug/m ³	<0.0025 ug	<0.16 ug/m ²
Methanol	FEP	<25 ug/m ³	<0.0063 ug	<0.39 ug/m ²
pH3 Buffer	PFA	<50 ug/m ³	<0.0125 ug	<0.78 ug/m ²
pH3 Buffer	FEP	<50 ug/m ³	<0.0125 ug	<0.78 ug/m ²
pH10 Buffer	PFA	<25 ug/m ³	<0.0063 ug	<0.39 ug/m ²
pH10 Buffer	FEP	<25 ug/m ³	<0.0063 ug	<0.39 ug/m ²

Note: Hexane data is not reported since the hexane blank was not clean enough to enable measurement of trace metals in the extracts. If ultrapure hexane were available, it may be assumed that metals extracted by hexane would be at concentrations similar to those found with methanol.

Summary

Purillex PFA and FEP bottles, manufactured from DuPont™ Teflon® resins, were subjected to a comprehensive extractables test protocol featuring five different extraction solutions, for extended periods at elevated temperatures. The test protocol simulated extreme storage and handling conditions, enabling a rigorous product-contact evaluation of Purillex PFA and FEP bottles.

Analysis of the extraction samples was carried out using some of the latest analytical instrumentation, covering a range of techniques. Analytical protocols for organic extractables covered the widest possible range of non-volatile, semivolatile and volatile compounds and none were detected in any of the solvents, for either bottle type. No extracted TOC was detected and conductivity measurements remained unchanged over 28 days. Analytical protocols for inorganic extractables employed state of the art ICP-QMS and HR-ICP-MS, operated in full quant mode, to measure all USP and ICH elements. The total amount of inorganic analytes extracted from the bottles was at the low ng level, corresponding to <1 ug/m² when expressed as total weight of extractables per contacted surface area.

Despite the aggressive extraction protocols used in the testing of Purillex PFA and FEP bottles, no extractable organic compounds were detected, and extractable inorganic compounds were measured at concentrations far below any level that may be stipulated by the various regulatory bodies around the world. The data and methodology contained in the associated complete test reports^{1,2}, available on request from Savillex (send an email request to info@savillex.com), may be used to support end user validation of Purillex PFA and FEP bottles for API product-contact applications.

References:

- 1.) 7-day and 28-day Extraction Results for Savillex PFA Bottles, DuPont, Wilmington, DE, USA. Jan 2014. (Available from Savillex Corporation).
- 2.) 7-day and 28-day Extraction Results for Savillex FEP Bottles, DuPont, Wilmington, DE, USA. Jan 2014. (Available from Savillex Corporation).

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