

The Effect of a Barrier Film on Elastomeric Extractables in a Parenteral Packaging System

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Abstract

Extractables from elastomeric components become an issue even before a pharmaceutical drug makes contact with the elastomeric component. The suitability of the elastomer and the drug product needs to be taken into consideration at the development stage of the packaging and delivery system for the drug product. The potential for an extractable to leach into the drug product and the impact that leachable will have on the drug's stability, efficacy and toxicity needs to be scientifically evaluated. A way to reduce the amount of extractables that could potentially leach into a drug product from an elastomeric closure is to utilize a fluoropolymer film. The fluoropolymer film reduces the closure-drug interaction there-by reducing the amount of leachables in the drug product. To demonstrate the effectiveness of the fluoropolymer film, multiple closures, laminated with fluoropolymer film and without, were sealed onto vials containing various solvents representing typical drug product solvent vehicles. As a worst-case scenario the vials were inverted and stored at 40°C/75% RH ($\pm 2^\circ\text{C}/5\%$ RH). Each set of vials/solvents was tested at time 0, 3 months and 6 months. The analytical techniques used to identify any leachables included Ion Chromatography (IC), Inductively Coupled Plasma Spectroscopy (ICP), and High Performance Liquid Chromatography utilizing Photodiode Array and Mass Spectrometry (LC/PDA/MS) and Gas Chromatography with Mass Spectrometry (GC/MS). The results from this study confirm that fluoropolymer film reduces leachables from the elastomeric closures.

Methodology

To make a direct comparison, a 20 mm chlorobutyl-synthetic isoprene blend serum closure, with and without fluoropolymer film was evaluated. Potential extractables for this closure include antioxidants, plasticizers, and other formulation-related compounds. The closures were autoclaved at 121°C for 30 minutes and then placed under a laminar flow hood until assembly. Ten milliliter capacity Type I glass vials were rinsed three times with purified water and allowed to dry in a laminar flow hood for 24 hours before assembly. Vials were filled with 10 mL of a pH

3.0 aqueous solution, neutral aqueous solution, pH 10.0 aqueous solution, 50% ethanol/purified water solution, 50% propylene glycol/purified water solution, and 0.03% Polysorbate 80/purified water solution. The vials were sealed with the appropriate closure and capped with an aluminum seal. For analysis of volatile extractables, vials of ambient air were sealed and capped. Time 0 samples were tested directly after sealing and capping. The solvent filled vials were inverted once before testing to allow the solvent to make contact with the closure. The remaining vials were stored inverted, as worst-case conditions with direct contact to the solution, at 40°C/75% RH ($\pm 2^\circ\text{C}/\pm 2\%$ RH). At Time 0 and each additional time pull, the contents of five vials were combined for each solution set.

Non-Volatile Residue:

Ten mL of each extract, except 0.03% Polysorbate 80, and blank was evaporated to dryness in tared evaporating dishes using a steam bath. The 0.03% Polysorbate 80 samples were first extracted with Methylene chloride and a portion of that extract was evaporated to dryness in tared evaporating dishes using a steam bath. The evaporating dishes were then placed in an oven at 105°C for 1 hour. The preparations were then cooled to room temperature and weighed.

For all samples, < 50mg of non-volatile residue was observed.

HPLC/PDA/MS:

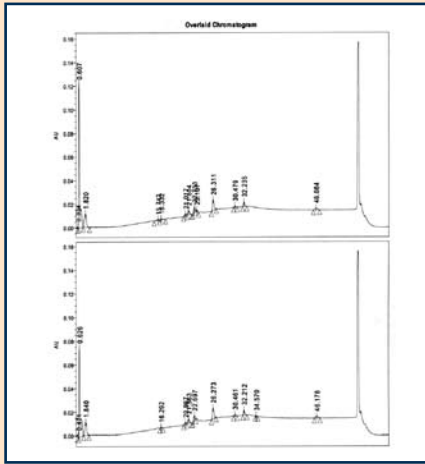
The non-volatile residues for all extracts except pH 3 were reconstituted as follows:

Extraction Solvent	Reconstituting Solvent
pH 7	Water
pH 10	Water
50% Ethanol/water	50% Ethanol/water
50% Propylene glycol	Acetonitrile
0.03% Polysorbate 80	Acetonitrile

GC/MS:

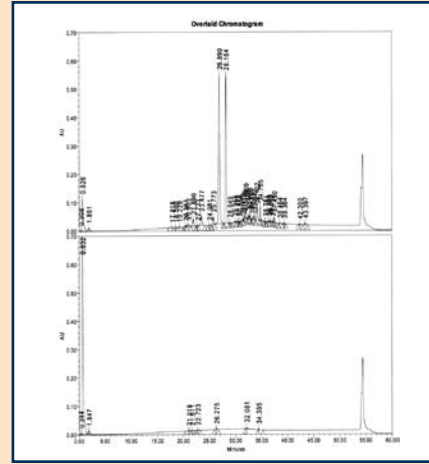
The pH3, pH 7, pH 10, 50% Propylene Glycol, and 50% Ethanol samples were extracted with equal amounts of Methylene chloride. The Methylene chloride extract was analyzed.

HPLC/PDA Overlay #1 –
Time 0, 50% Ethanol



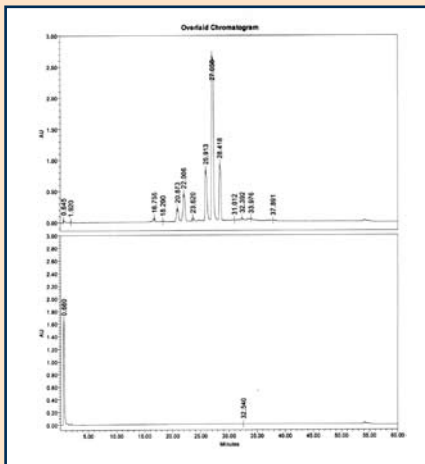
Top = without Fluoropolymer film Bottom = with Fluoropolymer film

HPLC/PDA Overlay #2 –
Time 3 Months, 50% Ethanol



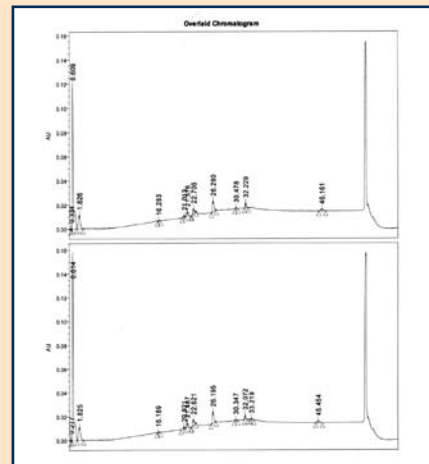
Top = without Fluoropolymer film Bottom = with Fluoropolymer film

HPLC/PDA Overlay #3 –
Time 6 Months, 50% Ethanol



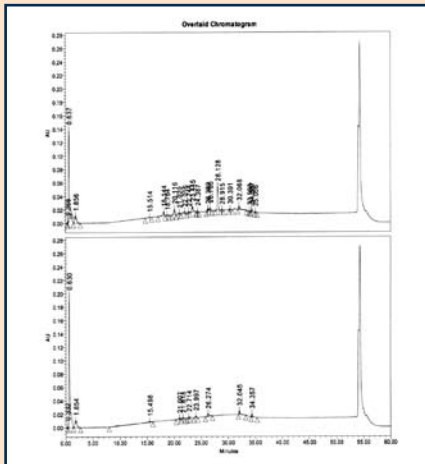
Top = without Fluoropolymer film Bottom = with Fluoropolymer film

HPLC/PDA Overlay #4 –
Time 0 Months, 50% Propylene Glycol



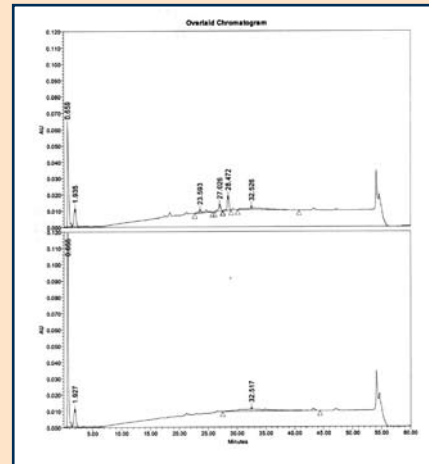
Top = without Fluoropolymer film Bottom = with Fluoropolymer film

HPLC/PDA Overlay #5 –
Time 3 Months, 50% Propylene Glycol



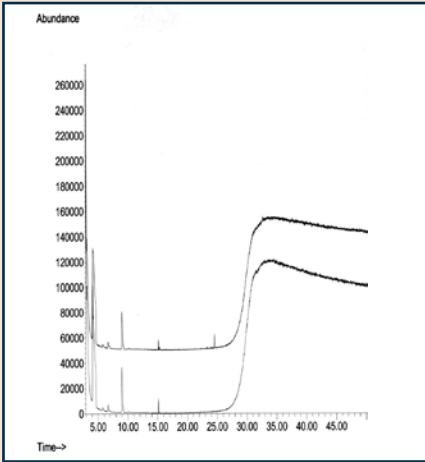
Top = without Fluoropolymer film Bottom = with Fluoropolymer film

HPLC/PDA Overlay #6 –
Time 6 Months, 50% Propylene Glycol



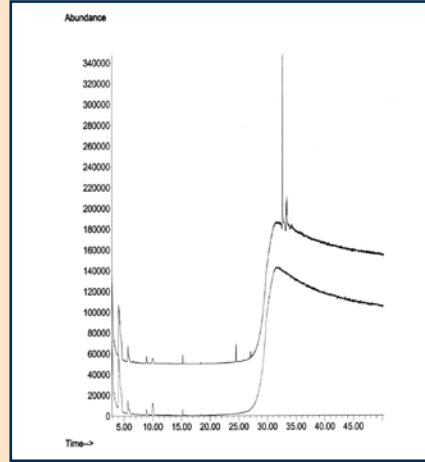
Top = without Fluoropolymer film Bottom = with Fluoropolymer film

GC/MS Overlay #1 –
Time 0, 50% Ethanol



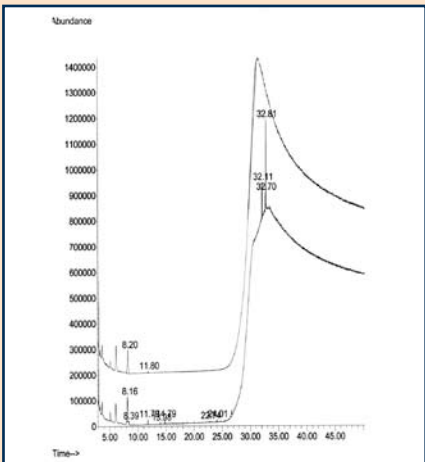
Top = without Fluoropolymer film Bottom = with Fluoropolymer film

GC/MS Overlay #2 –
Time 3 Months, 50% Ethanol



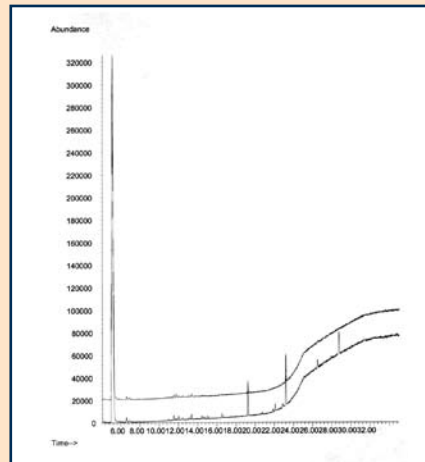
Top = without Fluoropolymer film Bottom = with Fluoropolymer film

GC/MS Overlay #3 –
Time 6 Months, 50% Ethanol



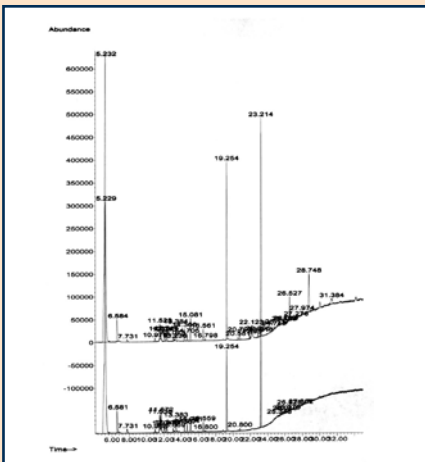
Top = with Fluoropolymer film Bottom = without Fluoropolymer film

GC/MS Headspace Overlay #1 –
Time 0



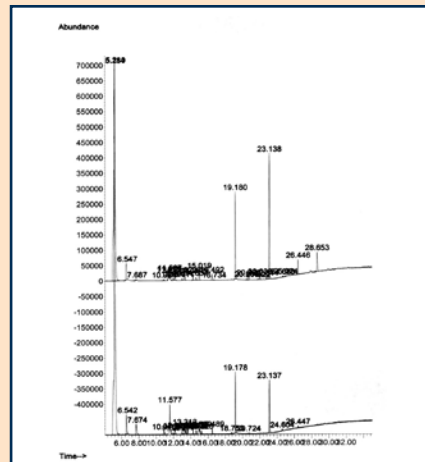
Top = with Fluoropolymer film Bottom = without Fluoropolymer film

GC/MS Headspace Overlay #2 –
Time 3 Months



Top = without Fluoropolymer film Bottom = with Fluoropolymer film

GC/MS Headspace Overlay #3 –
Time 6 Months



Top = without Fluoropolymer film Bottom = with Fluoropolymer film

GC/MS Headspace:

Two sealed vials of each of the samples, with and without the fluoropolymer film, were heated and the air within the sealed vial was removed with a syringe and injected into the GC/MS.

ICP:

Ten milliliters of the 0.03% Polysorbate and pH 3 extracts were evaporated to dryness and the residues were reconstituted with nitric acid.

IC:

The pH 7, pH 10, and 0.03% Polysorbate 80 extracts were analyzed neat.

Table I – ICP Results

ICP Results			
Sample	Amount of Calcium (ppm)		
	Time 0	3 Months	6 Months
pH 3 - Without Fluoropolymer Laminate	2.05	2.03	2.44
pH 3 - With Fluoropolymer Laminate	< LOQ	< LOQ	< LOQ
0.03% Polysorbate 80 - Without Fluoropolymer Laminate	< LOQ	1.57	2.06
0.03% Polysorbate 80 - With Fluoropolymer Laminate	< LOQ	< LOQ	< LOQ

LOQ = 1.000 ppm

Table II – IC Results

IC Results of 0.03% Polysorbate 80			
Sample	Amount of Chloride (ppm)		
	Time 0	3 Months	6 Months
Without Fluoropolymer Laminate	< LOQ	1.3	1.3
With Fluoropolymer Laminate	< LOQ	< LOQ	< LOQ

LOQ = 1 ppm

Conclusion

The results of this study show that the potential for extractables leaching into drug product solvent vehicles from closures is a reality. The LC and GC results show, antioxidants and other formulation-related compounds leached from the closures without fluoropolymer film into 50% ethanol/water and 50% propylene glycol/water solutions. These antioxidants and other formula-related compounds were not seen or were seen in reduced levels in the closures with the fluoropolymer film.

The ICP analysis showed quantifiable levels of calcium leached into the pH 3 and 0.03% Polysorbate 80 solutions from the closures without fluoropolymer film, while over the same period of time, no quantifiable level of calcium leached from the closures with the fluoropolymer film. The IC results show that chloride was detected from closures without the fluoropolymer film but not from the closures with fluoropolymer film after 3 and 6 month of storage at accelerated conditions.

Results

The results for each of the HPLC/PDA/MS, GC/MS and GC/MS Headspace are presented to the right as overlay chromatograms comparing the closure with and without fluoropolymer film.

The tables below detail the ICP and IC results for each of the studied solvents.

The pH 7 extracts did not show any leachables at these times.

The study revealed that even over a period of 6 months, leachables can be detected and there is a potential for those leachables to increase over time. It is important to not only look at what can leach from the closure but how much of that leachable can be detected and its effect on the drug product.

The methods used in this study are screening methods. Now that extractables have been identified, the next step is to develop and validate test methods in drug product. The leachables can then be quantified over the shelf life of the drug product.

Three key points to take from this study are that the use of a fluoropolymer film can greatly reduce the risk of leachables in a drug product, leachables can increase over even a short time period at accelerated conditions, and choosing the correct methods for analysis of leachables is critical.

Acknowledgements:

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