
One-Touch[®] Single-Use Systems

Film Extractables Comparison

TepoFlex[®], HyQ[®] CX5-14, Stedim 40 and 71

Rev 2.1

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Disclaimer

The data in this document is not intended to encompass all extractable compounds that could be present in the featured films. While the comparison of extractables between different films was solely based on literature review, they do provide insight in the presence or absence of certain target compounds and their respective quantification levels. However, this data can only serve as a general guide because not all extractable data sets have been conceived under exactly the same experimental conditions and analytical methods. It is important to note that according to the manufacturers all compared films have passed the requirements for biological safety per USP Class VI. It remains the responsibility of the end user to demonstrate compatibility of the specific product or solution under consideration with a film under actual process conditions used. Meissner Filtration Products, Inc. does not make any warranty or representation, express or implied, with respect to the accuracy, completeness or utility of the information contained in this document.

I. Introduction

Extractables originate from many sources including raw materials, residual solvents and catalysts used during polymer manufacturing, chemical additives to stabilize resins or to protect them from degradation, such as for example those resulting from the effects of gamma irradiation, or to impart certain properties, and processing aids to facilitate film conversion.

This film extractables report compares published extractables data for certain target compounds from four (4) commercially available films, i.e., three (3) PE-based (polyethylene) product contact films, TepoFlex[®] (Meissner Filtration Products), HyQ[®]CX5-14 (ThermoFisher), and Stedim 40 (Sartorius Stedim Biotech); and one (1) EVA-based (ethylene vinyl acetate) product contact film Stedim 71 (Sartorius Stedim Biotech).

A. Basis of Comparison

- *Disposable Flexible Container Systems for Cell Culture Media and Other Sterile Liquids, HyClone, Technical Paper Series, Revision 2, August 2004, SM0455.*

Test Method Summary

Test containers were filled with extraction fluid to obtain a surface area-to-liquid volume ratio of approximately 2 cm² / mL and held for 90 days at 40°C, unless otherwise indicated. These storage conditions equate to a real-time equivalent of roughly 8 months at ambient temperature per ASTM F1980-07.

The extraction fluids were: Water, PBS (phosphate buffered saline) pH 3, PBS pH 7, PBS pH 10, 1N HCl (hydrochloric acid), 1N NaOH (sodium hydroxide), 6M GndHCl (guanidine HCl), 20% ethanol, 10% DMSO (dimethyl sulfoxide) - stored frozen at -20°C and thawed for analysis, and 0.1% Tween. Various chromatographic methods were used to determine the presence and level of the following target leachable compounds: Acetate, formate, fatty acids and amides. Total Organic Carbon (TOC) analysis was done on all aqueous extracts.

The respective aggregate extractables results for each film used in this comparison are listed in the Appendix.

- *TepoFlex[®] Qualification Guide QGOT01-01.C, Meissner Filtration Products, December 2014.*

Test Method Summary

Test biocontainers were gamma irradiated at a dose of 25-35 kGy, filled with extraction fluid to obtain a surface area-to-liquid volume ratio of 0.5, 2 and 3.3 cm² / mL and held for 90-91 days at 40°C and 75% RH, except for 96% Ethanol which was stored at 25°C and DMSO which was stored frozen at -20°C. The 90-91 days storage conditions at 40°C equate to a real-time equivalent of roughly 8 month at ambient temperature per ASTM F1980-07.

The extraction fluids were: WFI (Water for Injection) and UPW (Ultra Pure Water), PBS pH 3, PBS pH 11, 3M NaCl (sodium chloride) in WFI, 96% ethanol, 1% Tween 80 in WFI, 10% DMSO in WFI, 0.1M H₃PO₄ (phosphoric acid, pH < 2 ± 0.5), and 0.5M NaOH (sodium hydroxide, pH ~14 ± 0.5). Various chromatographic analytic methods were used to analyze for leachable compounds.

The aggregate extractables results for TepoFlex[®] film used in this comparison are listed in the Appendix.

All aggregate extractables results were organized in the same data format for ease of comparison.

B. Film Extractables Comparison

a. Aqueous Solutions

Extraction Fluid: WFI/UPW ^, Water *						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex® ^		Fatty Acids	Formate	Acetate	TOC	
HyQ®CX5-14 *		Fatty acids Amides	Formate		TOC Acetate	
Stedim 40 *		Fatty acids Amides	Acetate Formate		TOC	
Stedim 71 *		Fatty acids Amides	Formate			TOC Acetate (> 10 ppm)

Extraction Fluid: PBS (pH 3)						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex®				Acetate	TOC	
HyQ®CX5-14			Formate Fatty acids Amides		TOC Acetate	
Stedim 40			Acetate Formate Fatty acids Amides		TOC	
Stedim 71		Fatty acids Amides			Formate	TOC Acetate (> 10 ppm)

Extraction Fluid: PBS (pH 7)						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex®	No data on this extraction fluid					
HyQ®CX5-14		Fatty acids Amides	Formate		TOC Acetate	
Stedim 40		Fatty acids Amides	Acetate Formate		TOC	
Stedim 71			Fatty acids Amides		Formate	TOC Acetate (> 10 ppm)

Extraction Fluid: PBS (pH 11) ^, PBS (pH 10) *						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex® ^			Fatty acids	TOC Acetate		
HyQ®CX5-14 *			Formate Fatty acids Amides		TOC Acetate	
Stedim 40 *			Acetate Formate Fatty acids Amides		TOC	
Stedim 71 *		Amides	Fatty acids		Formate	TOC Acetate (> 10 ppm)

Extraction Fluid: 0.1M H ₃ PO ₄ ^, 1N HCl *						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex® ^	Acetate Formate	Fatty acids	TOC			
HyQ®CX5-14 *	Fatty acids		Amides	Formate	TOC Acetate	
Stedim 40 *	Fatty acids	Acetate	Amides	Formate	TOC	
Stedim 71 *	Fatty acids	Amides			TOC Formate	Acetate (> 10 ppm)

Extraction Fluid: 0.5 M NaOH ^, 1N NaOH *						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex® ^	Acetate Formate	Fatty acids	TOC			
HyQ®CX5-14 *	Amides			Formate Fatty acids	TOC Acetate	
Stedim 40 *	Amides			Acetate Formate	Fatty acids	TOC (18 ppm)
Stedim 71 *	Amides				Formate Fatty acids	TOC (80 ppm) Acetate (38 ppm)

b. Salts

Extraction Fluid: 3M NaCl						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm
TepoFlex®			Acetate	Formate Fatty acids		
HyQ®CX5-14	No data on this extraction fluid					
Stedim 40	No data on this extraction fluid					
Stedim 71	No data on this extraction fluid					

Extraction Fluid: 6M GndHCl						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm
TepoFlex®	No data on this extraction fluid					
HyQ®CX5-14	Acetate (< 9 ppm) Formate (< 3 ppm) Fatty acids Amides					
Stedim 40	Acetate (< 9 ppm) Formate (< 3 ppm) Fatty acids Amides					
Stedim 71	Acetate (< 9 ppm) Formate (< 3 ppm) Fatty Acids Amides					

c. Organic Solutions

Extraction Fluid: Ethanol 96% ^, Ethanol 20% *						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex® ^		Fatty acids	Formate	Acetate		
HyQ®CX5-14 *		Fatty acids Amides	Formate		Acetate	
Stedim 40 *		Fatty acids Amides		Acetate Formate		
Stedim 71 *		Fatty acids Amides			Formate	Acetate (> 10 ppm)

Extraction Fluid: 1% Tween 80 ^, 0.1% Tween *						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex® ^					Formate Acetate	
HyQ®CX5-14 *		Amides	Formate		Acetate Fatty acids	
Stedim 40 *			Acetate		Formate Fatty acids Amides	
Stedim 71 *				Fatty acids Amides	Formate	Acetate (> 10 ppm)

Extraction Fluid: 10% DMSO						
Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
TepoFlex®		Fatty acids		Formate Acetate		
HyQ®CX5-14		Acetate Fatty acids Amides	Formate			
Stedim 40		Amides	Fatty acids		Formate (3 ppm)	Acetate (<9 ppm)
Stedim 71		Fatty acids Amides		Formate	Acetate	

C. Discussion

The aqueous solutions extractables results show that the EVA-based product contact film, i.e., Stedim 71, has higher extractable TOC and acetate levels as compared to any of the PE-based product contact films, i.e., TepoFlex[®], HyQ[®]CX5-14 and Stedim 40, except for the 1N HCl extraction fluid where the TOC levels were in the 1-5 ppm range for films compared. Due to the difference in polymer compositions between the product contact layers of EVA-based and PE-based films, higher TOC and specifically acetate extractables levels in EVA-based product contact films are to be expected. In general, TOC and acetate levels among the different PE-based product contact films display similar extractables profiles. The TepoFlex[®] film does not show fatty acids and amides extractables in WFI/UPW, PBS (pH 3), PBS (pH 11), 0.1M H₃PO₄ and 0.5M NaOH or their levels were undetected or below control, except in PBS pH 11 where fatty acids were below < 0.5 ppm. That is consistent with the fact that no slip agents and/or anti-block agents have been added in TepoFlex[®] film.

If used, slip agents and/or anti-block agents are added to the PE or EVA product contact resin during the film extrusion to convey slip and anti-block properties to the film surface. This lowers the film's coefficient of friction (COF) and overcomes its natural tackiness. Historically these properties have been sought after by converters as they aid in film processing by easing the interface with equipment and limiting film blocking, i.e., two plies adhering to one another, however the addition of these agents increases the extractables profile. During film manufacturing slip and anti-block agents solubilize in the amorphous melt, but as soon as the resin cools and begins to crystallize, the slip and anti-block agents are forced out of the solidifying polymer matrix due to their limited solubility in a process commonly referred to as blooming. Therefore, by design these additives migrate from the resin matrix to the surface of the film and so even when added at very low levels they represent a source of extractables by accumulating at the films fluid contact surface. Traditionally slip agents are based on unsaturated fatty acid amides, most commonly oleamide and erucamide. Oleamide is derived from mono-unsaturated C18 oleic acid, while erucamide is derived from mono-unsaturated C22 erucic acid. Erucamide is more widely used because it is derived from non-animal sources and has a higher melting point and higher heat resistance than oleamide. Stearamide is yet another fatty acid amide that is commonly used but since it does not function effectively in reducing COF, it is typically used in combination with oleamide or erucamide to achieve the desired balance of slip and anti-block characteristics in the film.

The salts extractable results are insufficient to allow for a comprehensive comparison and will not be discussed further.

The organic solutions extractable results show that the EVA-based product contact film, i.e., Stedim 71, has higher extractable acetate levels as compared to any of the PE-based product contact films, i.e., TepoFlex[®], HyQ[®]CX5-14 and Stedim 40, as expected. In general, formate and acetate levels among the different PE-based product contact films display similar extractables profiles despite the differences of concentrations when considering the ethanol and Tween extraction fluids, and the temperature differences when considering the DMSO extraction fluid, conditions which generally were more aggressive for the TepoFlex[®] testing regime. The TepoFlex[®] film does not show any quantifiable levels of amide or fatty acids extractables in 96% ethanol, and 1% Tween. This is consistent with the fact that no slip agents and/or anti-block agents have been added to the TepoFlex[®] film.

D. Conclusion

The extractables levels of acetate, formate and fatty acids target compounds of TepoFlex[®] film in WFI/UPW, PBS (pH 3), PBS (pH 11), H₃PO₄, NaOH and 96% ethanol extraction fluids are significantly lower than those of Stedim 71 film, and similar to those of HyQ[®]CX5-14 and Stedim 40. TepoFlex[®] film does not show extractable amides target compound levels which is contrary to the HyQ[®]CX5-14, Stedim 40 and Stedim 71 films. This is consistent with the fact that TepoFlex[®] film does not use slip agents and/or anti-block agents.

Appendix

Film Aggregate Extractables Results

TepoFlex® PE-based Product Contact Film

Data Source

TepoFlex® Qualification Guide QGOT01-01.C, Meissner Filtration Products, December 2014.

Test Method Summary

For WFI, PBS (pH 3), PBS (pH 11), 3M NaCl, 6M GndHCl, 96% Ethanol, and 1% Tween 80 model solvents, the test biocontainers were gamma irradiated at a dose of 26-32 kGy, filled with extraction fluid to obtain a surface area-to-liquid volume ratio of 0.5 cm² / mL and held for 91 days at 40°C and 75% RH, equating to a real time equivalent of 219 days at ambient temperature, except for 96% Ethanol which was stored at 25°C.

A second data set was conceived for UPW and 96% Ethanol model solvents, the test biocontainers were gamma irradiated at a dose of 25.0-35.4 kGy, filled with extraction fluid to obtain surface area-to-volume ratio's of respectively 2 cm² / mL and 0.5 cm² / mL and held for 91 days at 40°C and 75% RH, equating to a real time equivalent of 219 days at ambient temperature.

For 10% DMSO model solvent, the test biocontainers were gamma irradiated at a dose of 26-32 kGy, filled with extraction fluid to obtain a surface area-to-liquid volume ratio of 0.5 cm² / mL and held for 91 days at -20°C, equating to a real time equivalent of 6.5 days at ambient temperature.

For 0.1M H₃PO₄ (pH < 2 ± 0.5) and 0.5 NaOH (pH ~14 ± 0.5) model solvents, the test biocontainers were gamma irradiated at a dose of 26.8-34.9 kGy, filled with extraction fluid to obtain a surface-to-volume ratio of 3.3 cm² / mL and held for 90 days at 40°C, equating to a real time equivalent of 217 days a ambient temperature.

Aggregate Extractables Results

Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm
Aqueous Solutions						
WFI, UPW		Fatty acids	Formate	Acetate	TOC	
PBS, pH 3				Acetate	TOC	
PBS, pH 7	No data on this extraction fluid					
PBS, pH 11			Fatty acids	Acetate TOC		
1N HCl	No data on this extraction fluid					
0.1M H ₃ PO ₄	Acetate ¹ Formate ¹	Fatty acids	TOC			
0.5M NaOH	Acetate ¹ Formate ¹	Fatty acids	TOC			
Salts						
3M NaCl			Acetate	Formate Fatty acids		
6M GndHCl	No data on this extraction fluid					
Organic Solutions						
96% Ethanol		Fatty acids	Formate	Acetate		
1% Tween 80					Formate Acetate	
10% DMSO		Fatty acids		Acetate Formate		

¹ Could not be effectively monitored due to matrix interference

HyQ® CX5-14

PE-based Product Contact Film

Data Source

Disposable Flexible Container Systems for Cell Culture Media and Other Sterile Liquids, HyClone, Technical Paper Series, Revision 2, August 2004, SM0455.

Test Method Summary

Test containers were gamma irradiated, filled with extraction fluid to obtain a surface area-to-liquid volume ratio of approximately 2 cm² / mL and held for 90 days at 40°C unless otherwise indicated, equating to a real time equivalent of 217 days at ambient temperature. 10% DMSO was stored frozen at -20°C and thawed for analysis.

Aggregate Extractables Results

Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 0.5 ppm	0.5 – 1 ppm	1 – 5 ppm	5 – 10 ppm
Aqueous Solutions						
Water		Fatty acids Amides	Formate		TOC Acetate	
PBS, pH 3			Formate Fatty acids Amides		TOC Acetate	
PBS, pH 7		Fatty acids Amides	Formate		TOC Acetate	
PBS, pH 10			Formate Fatty acids Amides		TOC Acetate	
1N HCl	Fatty acids		Amides	Formate	TOC Acetate	
1N NaOH	Amides			Formate Fatty acids	TOC Acetate	
Salts						
3M NaCl	No data on this extraction fluid					
6M GndHCl	Acetate (< 9 ppm) Formate (< 3 ppm) Fatty acids Amides					
Organic Solutions						
20% Ethanol		Fatty acids Amides	Formate		Acetate	
0.1% Tween		Amides	Formate		Acetate Fatty acids	
10% DMSO		Acetate Fatty acids Amides	Formate			

Stedim 40

PE-based Product Contact Film

Data Source

Disposable Flexible Container Systems for Cell Culture Media and Other Sterile Liquids, HyClone, Technical Paper Series, Revision 2, August 2004, SM0455.

Test Method Summary

Test containers were gamma irradiated, filled with extraction fluid to obtain a surface area-to-liquid volume ratio of approximately 2 cm² / ml and held for 90 days at 40°C unless otherwise indicated, equating to a real time equivalent of 217 days at ambient temperature. 10% DMSO was stored frozen at -20°C and thawed for analysis.

Aggregate Extractables Results

Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 500 ppb	500 ppb – 1 ppm	1 – 5 ppm	5 – 10 ppm
Aqueous Solutions						
Water		Fatty acids Amides	Acetate Formate		TOC	
PBS, pH 3			Acetate Formate Fatty acids Amides		TOC	
PBS, pH 7		Fatty acids Amides	Acetate Formate		TOC	
PBS, pH 10			Acetate Formate Fatty acids Amides		TOC	
1N HCl	Fatty acids	Acetate	Amides	Formate	TOC	
1N NaOH	Amides			Acetate Formate	Fatty acids	TOC (18 ppm)
Salts						
3M NaCl	No data on this extraction fluid					
6M GndHCl	Acetate (< 9 ppm) Formate (< 3 ppm) Fatty acids Amides					
Organic Solutions						
20% Ethanol		Fatty acids Amides		Acetate Formate		
0.1% Tween			Acetate		Formate Fatty acids Amides	
10% DMSO		Acetate (< 9 ppm) Formate (< 3 ppm) Fatty acids Amides	Fatty acids			

Stedim 71

EVA-based Product Contact Film

Data Source

Disposable Flexible Container Systems for Cell Culture Media and Other Sterile Liquids, HyClone, Technical Paper Series, Revision 2, August 2004, SM0455.

Test Method Summary

Test containers were gamma irradiated, filled with extraction fluid to obtain a surface area-to-liquid volume ratio of approximately 2 cm² / ml and held for 90 days at 40°C unless otherwise indicated, equating to a real time equivalent of 217 days at ambient temperature. 10% DMSO was stored frozen at -20°C and thawed for analysis.

Aggregate Extractables Results

Extraction Fluid	Not Quantifiable	Undetected or Below Control	< 500 ppb	500 ppb – 1 ppm	1 – 5 ppm	5 – 10 ppm (> 10 ppm)
Aqueous Solutions						
Water		Fatty acids Amides	Formate			TOC Acetate (> 10 ppm)
PBS, pH 3		Fatty acids Amides			Formate	TOC Acetate (> 10 ppm)
PBS, pH 7			Fatty acids Amides		Formate	TOC Acetate (> 10 ppm)
PBS, pH 10		Amides	Fatty acids		Formate	TOC Acetate (> 10 ppm)
1N HCl	Fatty acids	Amides			TOC Formate	Acetate (> 10 ppm)
1N NaOH	Amides				Formate Fatty acids	TOC (80 ppm) Acetate (38 ppm)
Salts						
3M NaCl	No data on this extraction fluid					
6M GndHCl	Acetate (< 9 ppm) Formate (< 3 ppm) Fatty acids Amides					
Organic Solutions						
20% Ethanol		Fatty acids Amides			Formate	Acetate (> 10 ppm)
0.1% Tween				Fatty acids Amides	Formate	Acetate (> 10 ppm)
10% DMSO		Fatty acids Amides		Formate	Acetate	