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Extractables Isolated from Two Competitor Butyl Rubber Stoppers; A Comparative Study

Neil Pothier, Krysty Bonczek, Mark Kimball, Por-Kim Seng, Joseph St. Laurent

Chemic Laboratories Inc., Canton, MA 02021

Abstract

Bromobutyl rubber stoppers are routinely used as the closure unit for lyophilization vials housing drug product and the closure unit for vials housing sterile fill drug product. A qualitative and quantitative extraction study was completed evaluating the comparative extraction profile of two manufactured bromobutyl rubber stoppers (i.e., A sterilized stopper with a Teflon® coating and sterilized stopper with proprietary coating). Analytical investigations included the controlled extraction of the stopper materials with various organic solvents (i.e., USP Purified water, Isopropyl alcohol, Dichloromethane and 0.1% HNO_3) using standard refluxing techniques. Qualitative analysis methods referenced by USP <381> and Quantitative analysis methods developed by Chemic Laboratories were completed using a variety of chromatographic and spectral analysis techniques and parameters.

The concluding data provides a comparative overview of the similarities and differences between the two manufacturer's bromobutyl stopper materials.

Extraction Method

Randomly chosen, duplicate stoppers were added to the appropriate extraction medium at a ratio of 0.1-0.2g/ mL (as determined by the component thickness). The collected stoppers were subdivided into quarters using a pre-cleaned stainless steel razorblade and were transferred to individual glass-stoppered, appropriately sized Erlenmeyer flasks of USP type I glass. 150 mL of USP purified water was added and the materials were agitated for approximately 30 seconds. This wash procedure was repeated two consecutive times to remove any surface debris, discarding the wash each time. The washed samples were then transferred to suitable reflux extraction flasks, and the required amount of extraction medium (i.e. USP Purified water, Isopropyl alcohol, Dichloromethane and 0.1% HNO_3) was added to each. All test samples were extracted for up to 24 hours with the exception of those samples prepared for metal and mineral investigations which were refluxed in the presence of 0.1% HNO_3 for a period of 1 hr.

Analytical Techniques

Qualitative
- Nonvolatile residue (NVR)
- Fourier Transform Infrared Spectroscopy (FTIR)
- Total Organic Carbon Analysis (TOC)
- pH
- Nephlometry
- Reducing Agents

Quantitative
- High Performance Liquid Chromatography
  - Diode Array Spectroscopy (HPLC-DAD)
  - Mass Spectrometry (HPLC-MS)
  - Ion Chromatography (HPLC-IC)
- Gas Chromatography
  - Mass Spectrometry (GC-MS)
- Inductively Coupled Plasma Spectroscopy
  - Mass Spectrometry (ICP-MS)

Qualitative Analysis

NVR: Representative sample extracts (IPA & DCM) were transferred to suitable, acid-cleaned, tarred crucibles and the volatile matter evaporated on a steam bath. The net weight of the isolated residue was determined.

FTIR: Representative sample extracts (IPA) were serially evaporated onto a suitable zinc selenide window and the associated blank corrected spectra were obtained.

TOC: Representative sample extracts (USP Purified water) were transferred to suitable TOC analysis vials and assayed for total organic carbon.

pH: Representative sample extracts (USP Purified water) were transferred to suitable vessels and the initial and final solution pH was determined.

Nephlometry: Representative sample extracts (USP Purified water) were transferred to suitable vessels and the solution turbidity according to USP method <851> was determined.

Reducing Agents: Representative sample extracts (USP Purified water) were transferred to suitable vessels and titrated with 0.01 N iodine, using starch TS as the indicator.

Quantitative Analysis

HPLC-DAD-MS: Representative sample extracts (IPA & USP purified water) were transferred to amber glass vials and assayed using reverse phase HPCL-DAD-MS techniques. Analysis was completed using a Zorbax SB-C18 4.6 X 150 mm X 5 µm analytical column and a gradient elution profile from 95% aqueous (0.05% TFA/ in USP purified water) to 95% organic (Acetonitrile) over a period of 20 minutes and held at 95% acetonitrile for 10 minutes. Diode array spectrum data were obtained at 200, 254, and 280 nm respectively. All MS data was collected using positive and negative mode atmospheric pressure chemical ionization (APCI) interfaced with a Agilent 1100 quadrapole mass spectrometer and was used to provide identification data for those extracted analytes detected by the DAD.

HPLC-IC: Representative sample extracts (IPA & USP purified water) were transferred to amber glass vials and assayed using HPCL-IC techniques for extractable Br^-. Analysis was completed using a Dionex, ION Pac AS4A-SC 4.0 mm X 250 mm X 12 µm ion chromatography analytical column and an Altech Anion Suppressor cartridge (100 X 4.6 mm). Chromatographic elution was completed using an isocratic mobile phase comprised of 1.7 mm $NaHCO_3$/1.8mM Na_2CO_3 over a period of 8 Minutes.

GC-MS: Representative sample extracts (IPA & DCM) were transferred to amber glass vials and assayed using GC-MS (ion impact) techniques. Analysis was completed using a Restex RTX-5 (30 M X 0.25 mm X 0.25 µm film) analytical column and a thermo gradient program from from 40°C to 280°C over a period of 27 minutes. Mass spectrum data were obtained from 40 to 500 AMU respectively. All MS data was collected using a Agilent 5973 ion impact mass spectrometer interfaced with a Agilent 6890 gas chromatograph.

ICP-MS: Representative sample extracts (0.1% HNO_3) were transferred to 15 mL high density polypropylene screw cap test tubes and assayed using ICP-MS techniques. The presence of 68 elements were evaluated at a detection limit of approximately 10 ng/mL.. All MS data was collected using a Perkin Elmer Elan 5000 Inductively Coupled Plasma emission Mass spectrometer.

Results

Qualitative Assays	**Stopper coated** with Teflon® coating	**Stopper coated** with proprietary coating
NVR:	0.004% w/w	0.005% w/w
FTIR:	aliphatic hydrocarbons present	
TOC:	0.99 µg/g	0.66 µg/g
pH (Before & After Extraction)	7.0 / 7.6	7.0 / 8.1
Nephlometry:	0.73 NTU	0.39 NTU
Reducing Agents:	NA	NA

ICP-MS	**Stopper coated** with Teflon® coating µg/g	**Stopper coated** with proprietary coating µg/g
Boron	0.13	<0.1
Magnesium	6.1	1.0
Calcium	6.1	<0.1
Titanium	0.28	<0.1
Iron	0.61	<0.1
Zinc	0.51	0.47
Sodium	33	<0.1
Aluminum	0.66	0.16
Potassium	6.07	<0.1

GC-MS	**Stopper coated** with Teflon® coating (µg/g)		**Stopper coated** with proprietary coating (µg/g)	
	2 hrs	24 hrs	2 hrs	24 hrs
Unknown #3	3.7	4.3	7.6	8.0
1,3 Di-tert-Butylbenzene	ND	ND	6.0	ND
Unknown #5	2.5	3.0	ND	ND
2,4 Di-tert-Butylphenol	ND	ND	2.3	ND
2,6-Di-tert-butyl-4-methylphenol (BHT)	113	135	1.7	1.3
Unknown #8	203	230	167	184
Unknown #9	ND	1.6	ND	ND

HPLC-IC	**Stopper coated** with Teflon® coating (µg/g)		**Stopper coated** with proprietary (µg/g)	
	2 hrs	24 hrs	2 hrs	24 hrs
Bromide	5036	4423	ND	ND

HPLC-DAD-MS	**Stopper coated** with Teflon® coating (µg/g)		**Stopper coated** with proprietary (µg/g)	
	2 hrs	24 hrs	2 hrs	24 hrs
Irganox 1076	NA	5.2	NA	ND

Conclusion

Finished drug products stored in borosilicate serum and/or lyophilization vials (the container system) will be exposed to extractable analytes of varying classifications (i.e., Lubricants, Plasticizers, Antioxidants, Antistatic Agents, Impact Modifiers, etc). These extractables analytes originate from the elastomer stopper (i.e., the closure system) which over extended periods of time and under routine and/or accelerated storage conditions may in turn result in target leachable analytes. These leachable analytes can therefore adulterate the finished dosage product. The investigation completed here-in demonstrates that stopper components which appear visually comparable may be significantly different in their extractable profile. Furthermore one should conclude that the closure system must be fully characterized prior to use in a finished dosage container/ closure system.