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Comparison of Binary Alcohol/Water Solvent Systems to Blood for Extractions of Blood-Contacting Medical Devices

Mark Anderson Jordi*, Taryn Meade, Kevin Rowland, Chih-Hu Ho, Jordan Tocher, Weixi Liu

[1] Jordi Labs, 200 Gilbert St., Mansfield, Ma, 02048

*Corresponding Author:
*Mark Jordi:
200 Gilbert St.
Mansfield, MA 02048
508-966-1301
mjordi@rqmplus.com

Abstract

The analysis of extractables and leachables and subsequent risk assessment is an important aspect of the determination of biocompatibility for many medical devices. Leachable chemicals have the potential to pose a toxicological risk to patients, and therefore it is required that they be adequately characterized and assessed for potential safety concerns. One important consideration in the assessment of leachables is the choice of a suitable simulating solvent intended to replicate the use condition for the device and its biological environment. This aspect of study design is especially difficult for blood contacting medical devices due to the complexity of simulating the biological matrix. This publication reports a comparison of the extracting power of different binary solvent mixtures and saline in comparison with whole blood for a bloodline tubing set connected to a hemodialyzer. Ten different known extractables were quantified spanning a range of physicochemical properties and molecular weights. The results indicated that for low molecular weight analytes, a suitable exaggeration for whole blood can be obtained using a low

concentration ethanol/water mixture (≈20%) and in general extracted quantity increases with the concentration of alcohol cosolvent. For polyvinylpyrrolidone, the opposite trend was observed as solubility of the polymer was found to decrease with increasing alcohol concentration, resulting in lower extracted quantities at high alcohol concentrations. Analysis of ethanol/water concentrations in the extract solutions post extraction indicated no change in solvent composition.

Keywords: Extractables, Leachables, E&L, simulating solvents, medical devices, whole blood

Introduction

During the clinical use of a medical device, chemicals may leach from the device into the physiological tissues or media (e.g. drug product) with which the device has contact. These leachable chemicals have the potential to pose a toxicological risk to patients, and therefore are required to be adequately characterized and assessed for potential safety concerns **(1-3)**. In order for a comprehensive toxicological risk assessment to be conducted, it is necessary to simulate the chemical interactions between the medical device and associated physiological tissue, to ensure that the identities and quantities of potential leachable chemicals determined during extraction studies are sufficiently representative of those which could be present under clinical use conditions.

This concept is challenging in practice, given that the physiological tissues with which medical devices are in contact are generally not analytically amenable. Therefore, it is necessary to simulate the use condition of a medical device using an analytically expedient solvent. However, physiological tissues are complex matrices that are not straightforward to simulate. For example, circulating blood, which has direct contact with a range of medical devices, is comprised of water, proteins, inorganic ions, enzymes, hormones, and cells **(4)**, suggesting that the simulation of numerous unrelated properties is necessary for a representative solvent system in order to provide a robust set of chemical characterization data for blood contacting devices. To overcome this challenge, extractables studies are frequently conducted with multiple solvents (typically a polar, mid-polar and non-polar solvent) at elevated temperatures so that the totality of all conditions presumably would provide a suitable exaggeration of the relevant extraction conditions. Regulatory bodies have further encouraged the use of exhaustive extraction conditions in which multiple rounds of extraction are repeated until the final round of extraction

contains no more than 10% of the first round of extraction. The combination of strong solvents (mid-polar and non-polar), elevated temperatures and exhaustive conditions can often result in a strong exaggeration as compared to the use conditions. If this exaggeration is too strenuous, it may result in an unfavorable conclusion regarding device safety which can then require further studies to resolve the residual risk. One way to address this residual risk is through the use of simulating solvents which are designed to provide a more similar extraction environment as compared to the actual use condition.

Considerations for selection of simulating solvents predominantly include pH, polarity, and ionic content **(5-7)**. Particular emphasis has historically been placed on polarity for selection of solvents to simulate blood contact **(8-9)**, leading to extensive use of binary alcohol/water mixtures as extraction solvents for devices with direct blood contact, with some literature support. Jenke et. al compared the extraction power of ethanol/water mixtures to a range of drug products, blood and blood fractions, and lipid solutions, and developed a simulating solvent strength model to predict an appropriate ratio of ethanol/water for simulation of different matrices **(10)**. The authors predicted that an ethanol/water ratio of 46/54 would provide a simulation of blood and blood fractions. In another study, Haishima and coworkers compared the extracting power of bovine serum to that of ethanol water mixtures (0-20% ethanol) and concluded that a 17.2% ethanol mixture was a suitable simulant for extraction of Bisphenol A **(11)**. Luo, et al. studied the extraction of di(2-ethylhexyl) phthalate (DEHP) from polyvinyl chloride (PVC) devices in blood and in a 37% ethanol/water mixture and concluded that the ethanol mixture was an exaggerated condition in comparison to blood **(12)**. Li used the Abraham general solvation model to estimate the solvent composition which was most equivalent to blood in solvation properties and concluded that ethanol/water (60/40, V/V) and ethanol/water (50/50,

V/V) could be used as blood simulating solvents in chemical characterization studies of medical devices **(13)**. On the basis of these studies and historical precedent, the ISO 10993 standard for *Biological Evaluation of Medical Devices – Part 18: Chemical Characterization of medical device materials within a risk management process* (2020) recommends that "a mixture of ethanol in water could be an appropriate simulating vehicle" for devices which have contact with circulating blood **(14)**.

However, the data supporting this recommendation of the use of binary solvent systems for the simulation of blood is limited, particularly with respect to the range of chemicals studied, rendering this approach subject to frequent scrutiny by regulatory bodies. Furthermore, representatives of regulatory bodies have expressed concerns regarding the potential for alcohols to react with leachable chemicals of interest, and have additionally posited that the alcohol constituent of a binary mixture may be selectively absorbed by polymeric materials of construction of a device, resulting in a change in composition of the extraction mixture **(15)**.

The objective of this paper is to evaluate the ability of ethanol/water binary mixtures to extract compounds from various medical devices at levels comparable to those extracted by blood or serum and to determine the stability of binary mixtures during extraction. To accomplish this, a group of commonly observed and toxicologically relevant chemicals were examined with a range of properties and source polymers. Additionally, this work aimed to investigate the validity of concerns expressed by regulators regarding the potential reactivity or selective partitioning of the alcohol constituent of these binary mixtures.

The study included recirculation extraction under typical clinical use conditions of two devices which have extracorporeal contact with circulating blood, namely a hemodialyzer and a bloodline tubing set, using bovine blood, normal saline, and a series of ethanol/water mixtures

ranging from 10% to 70% ethanol. These devices are comprised of a range of polymeric materials of construction including many of the major material types commonly used in medical devices, as listed in Table I. The resulting extracts were analyzed for a predefined set of target leachables expected from the materials of construction, and the results compared to determine the solvent system that most closely simulates blood in terms of observed levels of extracted chemicals. The target leachables, listed in Table II, were selected to represent a range of analyte polarity (LogP -0.1 to 11.7), molecular weight, volatility, and ionizability. Analysis was performed using a range of techniques, including gas chromatography with mass spectrometry (GC-MS), liquid chromatography with mass spectrometry (LC-MS), and gel permeation chromatography (GPC).

Furthermore, in a separate study, a range of additional devices were extracted in ethanol/water mixtures (20%, 50%, and 70% ethanol respectively), and the solvent composition was measured prior to and following the extraction to determine whether the alcohol content had decreased during the extraction process.

Materials and Methods

Chemical Reagents and Materials

An electron-beam sterilized hemodialyzer and ethylene oxide sterilized bloodline tubing set were used as representative device types for extraction. Both devices are legally marketed for hemodialysis treatment in the United States. Additionally, a nasal pillow, an ostomy skin barrier, a balloon wedge pressure catheter, and a urethral stent were extracted for the purpose of evaluating solvent composition. The primary materials of construction of each device type are listed in Table I. The standards used for targeted quantitation were obtained from commercial sources in high purity. The targeted analytes are listed in Table II.

Pooled bovine blood was obtained from Densco Marketing, Inc. (Woodstock, IL, USA) (blood draw date 5/17/2021), and was filtered, anticoagulant (heparin) was added and it was used for extraction within 24 hours. Ethanol supplied by Sigma Aldrich Co. (St Louis, MO, USA) (lot SHBG6698V) was mixed with water for injection to create binary solvent systems, and 0.9% Sodium Chloride, USP supplied by Fresenius Medical Care (Ogden, UT, USA) (lot 21AU06011) was used for the saline extractions.

Standard Preparation

Preparation of Stock and Working Standards for Small-Molecule Spiking: Approximately 20 mg of each standard was weighed out on an analytical balance into a 20 mL scintillation vial. Each standard was then dissolved in the appropriate amount of methanol (diluent) to result in a concentration of 2 mg/mL (approximately 10 mL). A 1 µg/mL solution (spiking solution) was prepared by combining an aliquot of all stock solutions in the appropriate amount of diluent. This solution was then further diluted to 1, 5, 10, and 50 ng/mL solutions.

Preparation of Stock and Working Standards for PVP Spiking: Approximately 10 mg of 1300k MW polyvinylpyrrolidone (PVP) was weighed out on an analytical balance into a 20 mL scintillation vial. The PVP was then dissolved in the appropriate amount of water (approximately 10 mL) to create a 1 mg/mL solution. The solution was placed on a shaker overnight to complete the dissolution. This stock solution was used for spiking and aliquots were further diluted to 5, 10, 25, 50, and 100 µg/mL for use in the construction of a GPC calibration curve.

Extraction Methods

The recirculation extraction used for comparison of target leachables in blood, saline, and ethanol/water mixtures was performed by connecting a bloodline tubing set to a hemodialyzer and to a glass solvent reservoir to create a closed circuit containing one liter of the extraction

vehicle. A motorized blood pump (external to the fluid pathway) was used to recirculate fluid. The extraction was performed in an incubator calibrated to 37□ for a duration of five hours in order to provide a worst-case simulation of typical chronic hemodialysis treatment conditions. Extractions were performed in triplicate, using a new set of devices and extraction vehicles for each replicate. No visible degradation of the devices was observed.

A separate set of submersion extractions were performed for the solvent composition study. Devices were submerged in the ethanol/water solvents at 50□ for a duration of 72 hours, which is an extraction condition used for numerous device types in alignment with ISO 10993-12:2021 Biological Evaluation of Medical Devices – Part 12: Sample Preparation and Reference Materials **(16)**. No visible degradation of the devices was observed.

Extract Preparation

Preparation of Whole Blood Samples for Small-Molecule Analysis: Two (2) mL aliquots of whole bovine blood were dispensed into 20 mL glass scintillation vials. Samples were spiked with the indicated quantity of the analyte and shaken. Eight mL of methanol was then added and the resulting precipitated suspensions were vortexed for 30 seconds. The samples were then incubated at room temperature for approximately 15 minutes. To achieve a more robust precipitation, the samples were then stored in a 2-8 ºC refrigerator overnight. The cold suspensions were then centrifuged at 3000 rpm for 10 minutes. The supernatant was removed and subjected to immediate analysis. If decantation was poor, the injection vials were centrifuged an additional time at 3000 rpm for 10 minutes. This process introduces a dilution factor of five (5).

Preparation of Whole Blood Samples for PVP Analysis: Two (2) mL aliquots of whole bovine blood were dispensed into 20 mL glass scintillation vials. Samples were spiked if needed

and shaken. Four mL of methanol followed by 4 mL of acetone was then added and the resulting precipitated suspensions were vortexed for 30 seconds. The samples were then incubated at room temperature for approximately 15 minutes. To achieve a more robust precipitation, the samples were then stored in a 2-8 ºC refrigerator overnight. The cold suspensions were then centrifuged at 3000 rpm for 10 minutes. The supernatant was removed and subjected to immediate analysis. If decantation was poor, the injection vials were centrifuged an additional time at 3000 rpm for 10 minutes. This process introduces a dilution factor of five (5).

Headspace GC-MS Analysis

Confirmation of ethanol concentration in the prepared alcohol water mixtures both before and after extraction were determined by Headspace GC-MS using an Agilent 6890 system using flame ionization detection (FID) (Agilent Technologies, Santa Clara CA). Separation was performed using a DB-624 capillary column (60m × 0.25 mm × 1.4 µm; Agilent Technologies, Santa Clara CA).

GC-MS Analysis

The concentration of cyclohexanone was determined using GC-MS. Analysis was performed using an Agilent 7890 system using a 5977 MSD (Agilent Technologies, Santa Clara CA). The detector was operated using electron ionization (EI) mode. Separations for determination of cyclohexanone concentration were performed using a DB-WAX capillary column (30m × 0.25 mm × 0.25 µm; Agilent Technologies, Santa Clara CA).

LC-MS Analysis

The concentration of caprolactam, myristic acid and 4,4’-methylenedianaline were determined using LC-MS. Analysis was performed using an Agilent 1290 HPLC system coupled with a 6470 MSD (Agilent Technologies, Santa Clara CA). Separation was performed using an

Eclipse Plus C8 analytical column (2.1 mm × 50 mm, 1.8 µm particle size; Agilent Technologies, Santa Clara CA).

LC-FLD Analysis

The concentration of bisphenol A (BPA) and related analogues was determined using HPLC with fluorescence detection. An Agilent 1290 HPLC system equipped with a fluorescence detector (FLD; G1321C; Agilent Technologies, Santa Clara CA) was used. Separation was performed using an Eclipse Plus C8 analytical column (2.1 mm × 50 mm, 1.8 µm particle size; Agilent Technologies, Santa Clara CA).

LC-UV Analysis

The concentration of Di-(2-ethylhexyl) phthalate and trioctyltrimellitate was determined using HPLC with UV detection. An Agilent 1200 HPLC system equipped with a diode array detector (DAD; G1315D; Agilent Technologies, Santa Clara CA) was used. Separation was performed with and Eclipse Plus C8 column (4.6 mm × 150 mm, 3.5 µm particle size; Agilent Technologies, Santa Clara CA).

GPC Analysis

Concentration of PVP was determined using GPC with UV detection. An Agilent 1100 HPLC system (Agilent Technologies, Santa Clara CA) was applied equipped with a diode array detector (G1315A; Agilent Technologies, Santa Clara CA). Separation was performed using a Phenomenex GFC P2000 analytical column (7.8 mm x 300 mm; Phenomenex, Torrence CA). A mobile phase consisting of 0.1M NaCl in 20% methanol (*aq.*) was used under isocratic conditions.

Data Processing

Data processing was performed using MassHunter Quantitative Analysis Version 10.1 (Agilent Technologies, Santa Clara CA) or JordiGPC version 2.0.0.4. Calibration was performed using signals specific to the analyte under study, including retention time and mass spectral confirmation with authentic reference standards. For UV quantitation, retention time with authentic reference standards was used to confirm peak assignment and background signals were confirmed to be absent through analysis of controls. Linear calibration was performed using signals integrated from the collected data. Table II includes the signals used for each analyte.

Results and Discussion

Comparison of Extractables in Blood, Saline, and Ethanol/Water Solvents

A summary of results for each compound targeted in the blood, saline, and ethanol/water extracts is included in Table III and shown graphically in Figures 1-5. Method accuracy was verified using spike and recovery experiments with a reference standard of each targeted analyte and determined to be within an acceptable range (85-115%). The exception to this was 4,4-methylenedianiline, which showed modest spike recovery of 46% in blood, but which was detected at quantifiable levels in the blood extracts. This suggests interaction between the blood matrix and this analyte. In addition, myristic acid was present at significant levels in the blood matrix (background component), and therefore did not yield meaningful spike and recovery data. Nevertheless, on the basis of these spike and recovery experiments for the remaining targeted analytes, it can be concluded that the methods were capable of accurately detecting and quantifying the analytes of interest in all solvent systems if they were present in the extracts above the detection limit.

The results indicate that the trend of targeted compound quantities extracted varied according to chemical properties. The small molecule analytes were generally extracted in greater quantities with increasing alcohol percentage, with the exception of highly polar compounds (hydrophilic). The highly lipophilic compounds showed minimal extraction in all but the 70% ethanol solvent. In contrast, PVP, the polymeric extractable, showed decreasing extracted quantities with increasing alcohol concentration due to its strong hydrophilicity. The extracted quantity for each compound as a function of solvent composition is illustrated in Figures 1-5. In most cases, the levels of compounds extracted in blood were minimal or below the limits of quantitation. The two compounds which were found to be extracted in blood were caprolactam and 4,4-methylenedianiline. These two compounds were the most polar compounds analyzed with log P values -0.1 and 1.6. Blood was effective only for extraction of polar compounds. The detected levels in blood were comparable in all cases to the lower percentages of ethanol in water (10% or 20% ethanol/water). On the basis of these results, an ethanol/water mixture in the region of 20% provided a reasonable worst-case simulation of blood in terms of extraction propensity for the range of chemicals studied, including molecules ranging in polarity, molecular weight, volatility and ionizability. Furthermore, the results show that increasing the alcohol concentration in the extraction solvent provides, in some cases, a significant exaggeration of extracted compound quantities in comparison to blood, and in other cases, a significant underestimation. Therefore, the use of a high concentration alcohol solvent should not be expected to universally provide an appropriate, or even an exaggerated, simulation of blood contact. It is noted that the percentages of alcohol which resulted in the most similar results to blood in this study were lower than in some but not all other reports **(10-13)**. This may be a result of the fact that, in those studies, more exaggerated extraction conditions (higher temperatures or

longer times) were applied presumably allowing for equilibrium concentrations of leachables to be reached. This is not however consistent with the use conditions for the device, as applied in this study, allowing a comparison of the actual leachable quantities while contrasting the extraction media. The data presented supports that higher alcohol contents would increase the extracted quantities of most (especially hydrophobic) chemicals, but it was also noted to result in reduced extractable quantities for PVP. Therefore, higher alcohol content does not result in an exaggerated condition for all compounds and the most similar solvent is preferred.

Solvent Composition

The results of the solvent composition measurements are included in Table IV and Table V. These results demonstrate that the concentrations of ethanol in the extracts after the extraction is complete are comparable to the concentrations in the stock solution (both refrigerated and heated) prior to extraction for all devices tested. This indicates that selective adsorption of the organic constituent (alcohol) by the device materials did not occur for the range of materials included in this study on a scale sufficient to cause bulk solution composition change. A publication by Sussman, et al., cited work by Feng and coworkers to support the contention that absorption of alcohols can lead to bulk changes in the composition of extraction solvents (specifically alcohol water solutions) on a scale sufficient to influence extraction behavior and that these solvents should therefore be avoided **(3, 17)**. The results presented here do not support that contention and it is noted that Feng and coworkers were examining the phenomena of pervaporation through a polymer membrane. Feng and coworkers noted that “Pervaporation transport is usually described to be a three-step process: solution-diffusion-evaporation.” In an extractables or leachables study, the medical device should be extracted in an enclosure that does not allow for evaporation and hence pervaporation should not be possible. This then limits the

potential for selective absorption (solvent composition change) to only that quantity which can be readily absorbed (but not evaporated from) the medical device which explains the differences observed in these results.

Conclusion

Using a range of target compounds with varying chemical properties, it has been demonstrated that blood showed minimal extraction for all but the most polar analytes. This indicates that solvent systems with a higher percentage of alcohol or non-polar organic constituents may not yield a clinically relevant extraction profile for devices which have contact with blood. In this study, a solvent system comprising approximately 20% ethanol in water provided a reasonable worst-case simulation of the extracting power of blood. Since selective absorption of the alcohol constituent of binary mixtures can be ruled out, these solvent systems are deemed suitable in terms of consistency during the extraction process subject to verification. Furthermore, no reactions between targeted analytes and ethanol were observed for the range of chemical properties evaluated in this study, as indicated by acceptable spike recovery results of reference standards.

Conflict of Interest Declaration

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Tables

Table I Devices used for extraction and associated materials of construction

Device	Primary Materials of Construction	Study Purpose
Hemodialyzer	Polycarbonate, Polysulfone, Polyurethane, Silicone	Comparison of target leachables in blood, saline, and ethanol/water mixtures
Bloodline tubing set	Plasticized PVC, Acrylonitrile butadiene styrene (ABS), Nylon	Solvent composition measurement
Nasal Pillow	Polydimethylsiloxane	Solvent composition measurement
Ostomy skin barrier	Ethylene vinyl acetate, Polyisoprene	
Balloon wedge pressure catheter	Polyurethane, Polyethylene, Polyisoprene	
Urethral stent	Poly(ethylene:propylene)	

Table II Targeted Analytes with associated chemical properties and analytical methods

Analyte	CAS RN	Notable Chemical Properties	Analytical Method for Quantitation	Signal
Caprolactam	105-60-2	Highly polar (LogP -0.1)	LC-MS	MRM (114.1->42.2)
4-4-Methylenedianiline	101-77-9	Basic, polar (LogP 1.6)	LC-MS	MRM (199.0->106.1)
Bisphenol A Monomethyl ether-Bisphenol A Dimethyl ether-Bisphenol A	80-05-7 16530-58-8 1568-83-8	Mid-polar (LogP 3.1, 3.4, 3.7 respectively)	LC-FLD	FLD (Ex=225 nm; Em=310 nm)
Di-(2-ethylhexyl) phthalate	117-81-7	Non-polar (LogP 7.6)	LC-UV	DAD (210 nm)
Trioctyltrimellitate	3319-31-1	Highly non-polar (LogP 11.6)	LC-UV	DAD (210 nm)
Cyclohexanone	108-94-1	Polar (LogP 0.8), volatile	GC-MS	SIM 98.0 u
Myristic acid	544-63-8	Acidic, Mid-polar (LogP 5.3)	LC-MS	SIM 272.2 u
Polyvinylpyrrolidone	9003-39-8	Polymer	GPC	DAD 226 nm

Table III Summary of Targeted Quantitation Results for Blood and Solvent Extraction Study

Targeted Analyte	Concentration of Analyte (µg/device)					
	Blood	Saline	10% Ethanol	20% Ethanol	40% Ethanol	70% Ethanol
Caprolactam	27.34 ± 0.83	21.48 ± 0.73	24.18 ± 0.17	24.68 ± 1.71	35.04 ± 1.92	31.10 ± 1.29
4-4-Methylenedianiline[1]	0.63± 0.07[1]	<0.10	2.17 ± 0.26	4.88 ± 0.94	21.7 ± 0.99	89.37 ± 10.00
Bisphenol A	<10	<10	<10	0.8 ± 0.2	28.8 ± 4.7	50.5 ± 5.5
Bisphenol A Monomethyl ether	<10	<10	<10	<10	4.9 ± 0.6	7.6 ± 0.8
Bisphenol A Dimethyl ether	<10	<10	<10	<10	11.8 ± 1.9	296.2 ± 68.2
Di-(2-ethylhexyl) phthalate	<500	<100	<100	<100	<100	1161 ± 389
Trioctyltrimellitate	<500	<100	<100	<100	<100	3631 ± 381
Cyclohexanone	<20	30 ± 5	154 ± 8	140 ± 45	269 ± 72	243 ± 31
Myristic acid	*elevated in background	1.43 ± 0.17	3.04 ± 0.36	5.21 ± 1.29	55.02 ± 6.93	126.18 ± 15.88
Polyvinylpyrrolidone[2]	<35	37.3 ± 6.3	43.4 ± 9.6	26.9 ± 6.2	19.6 ± 5.9	5.9 ± 1.1

Samples were analyzed in triplicate. Average and standard deviation are reported.

[1] Low recovery was observed for this analyte in blood.

[2] Values are reported in mg/device.

Table IV Measured Solvent Composition of Ethanol/Water Mixtures Before and After Extraction

Sample Type	20% Ethanol in water	50% Ethanol in water	70% Ethanol in water
Refrigerated Stock Solution	19.8%	48.6%	66.9%
Heated Stock Solution	19.4%	47.6%	67.3%
Nasal pillow	21.4%	49.4%	70.5%
Ostomy skin barrier	22.8%	49.7%	70.3%
Balloon catheter	20.2%	49.9%	69.7%
Urethral stent	19.4%	48.0%	69.1%
Average of duplicate measurements of a single sample preparation.			

Table V Measured Solvent Composition of Ethanol/Water Mixtures After Dialyzer and Tubing Set Extraction

Sample Type	10% Ethanol in water	20% Ethanol in water	40% Ethanol in water	70% Ethanol in water
Hemodialyzer and bloodline tubing set recirculation extraction	9.9%	18.4%	37.4%	65.6%
Samples were analyzed in triplicate and the average value reported.				

Figure Captions

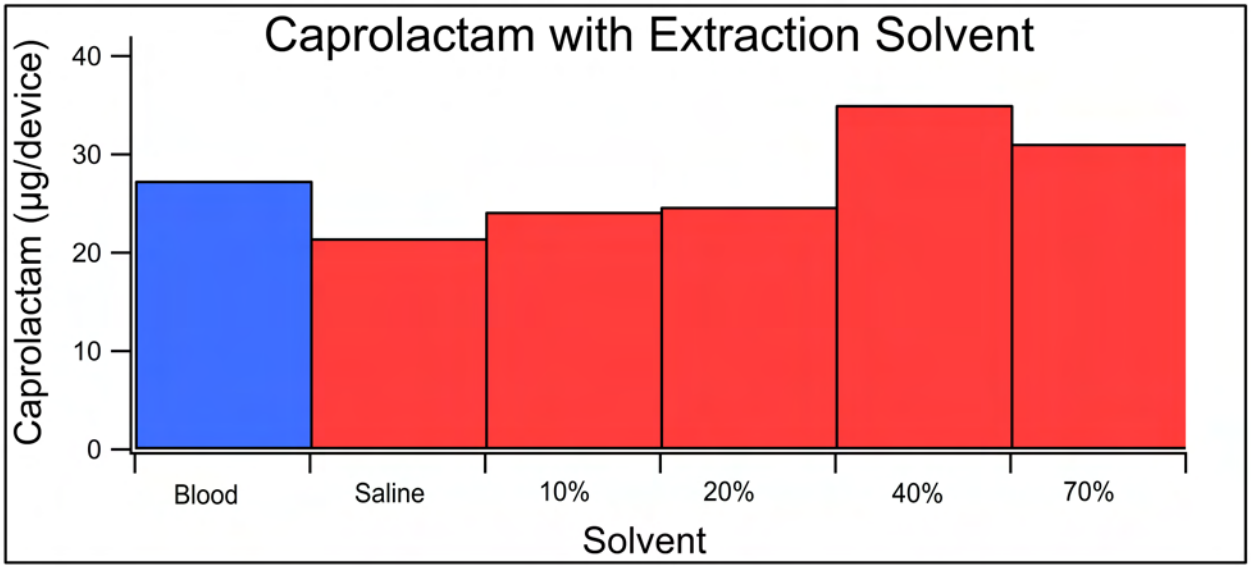
Figure 1: Extraction trends of Polar Extractables

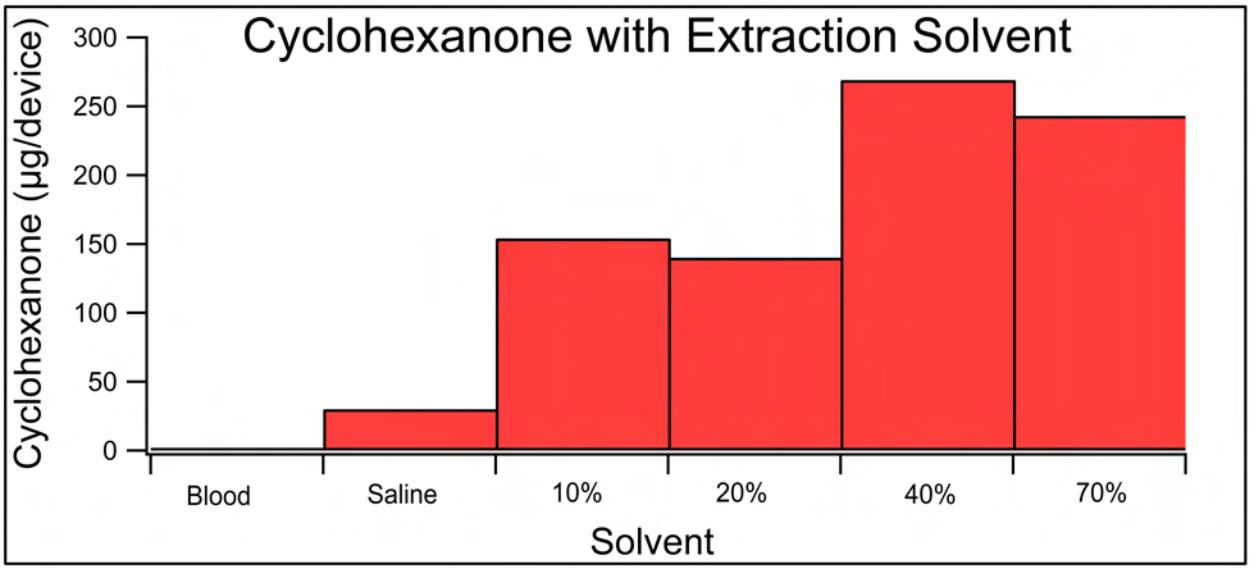
Figure 2: Extraction trends of Acidic and Basic Extractables

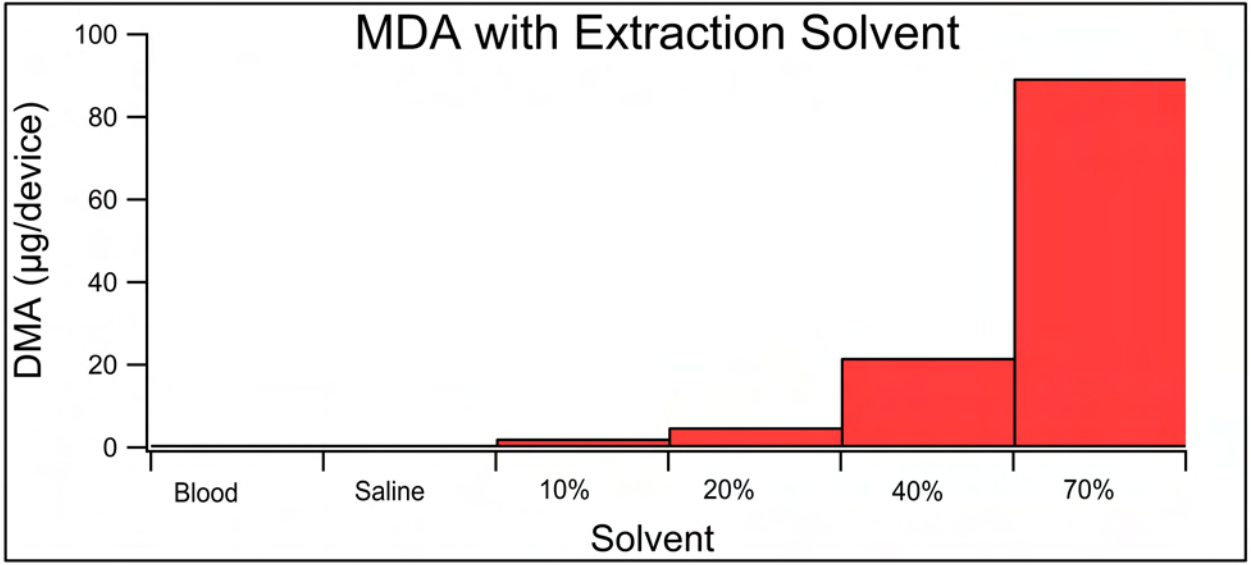
Figure 3: Extraction trends of Mid-Polar Extractables

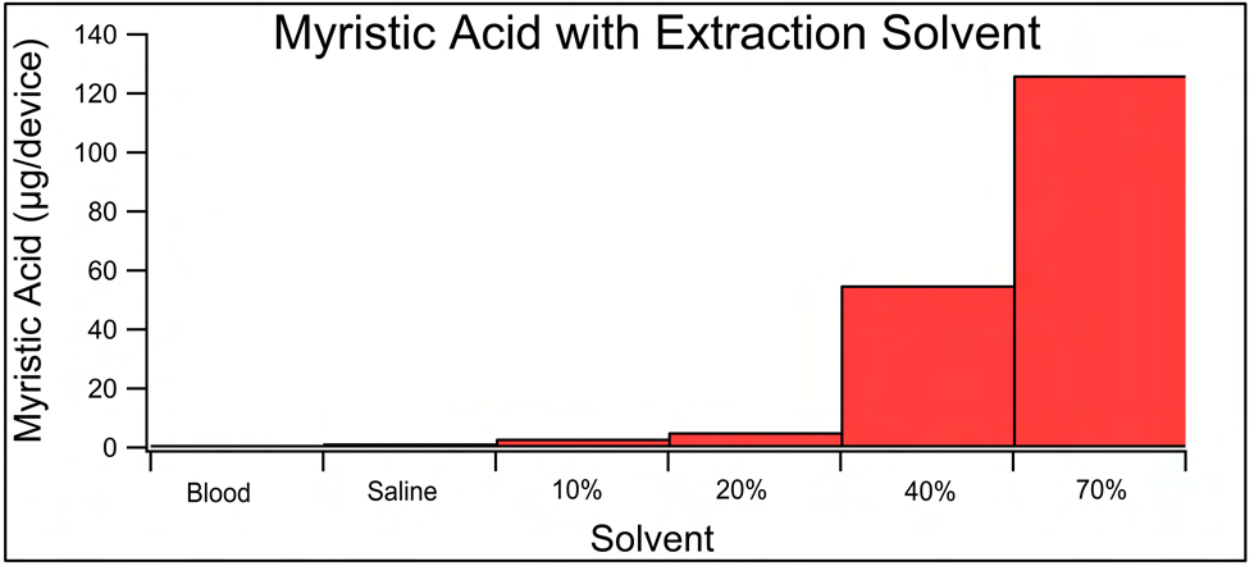
Figure 4: Extraction trends of Non-Polar Extractables

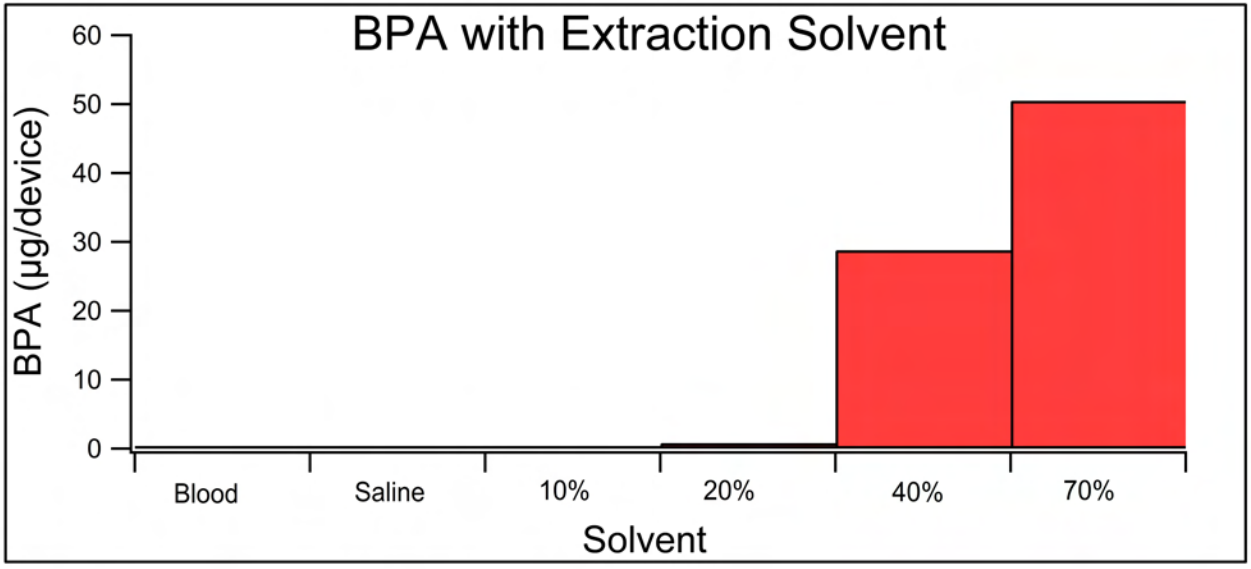
Figure 5: Extraction trend of Polymeric Extractable (Note that blue indicates that the value was less than this level in the indicated extraction solvent)

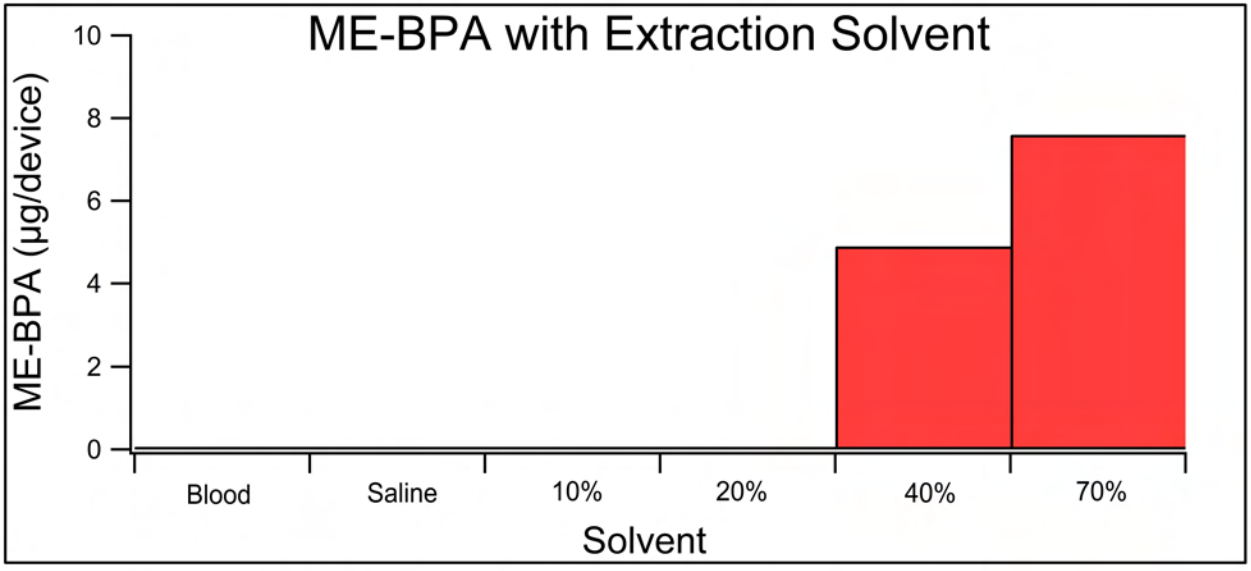

Caprolactam with Extraction Solvent
Caprolactam (µg/device)
40
30
20
10
0
Blood
Saline
10%
20%
40%
70%
Solvent

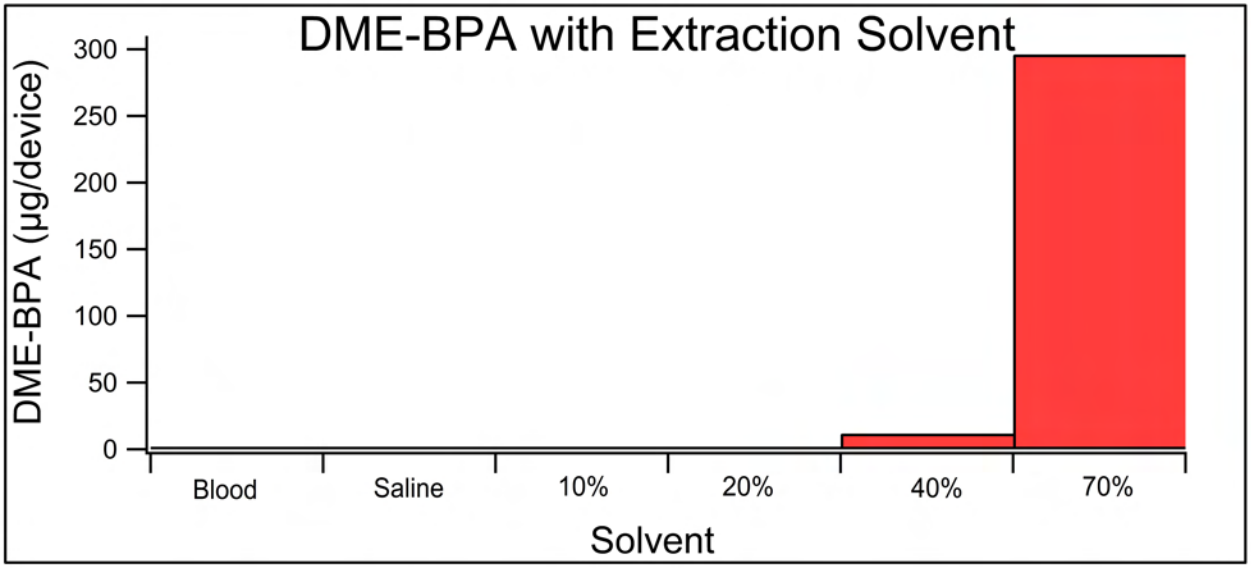

Cyclohexanone with Extraction Solvent
Cyclohexanone (µg/device)
300
250
200
150
100
50
0
Blood
Saline
10%
20%
40%
70%
Solvent

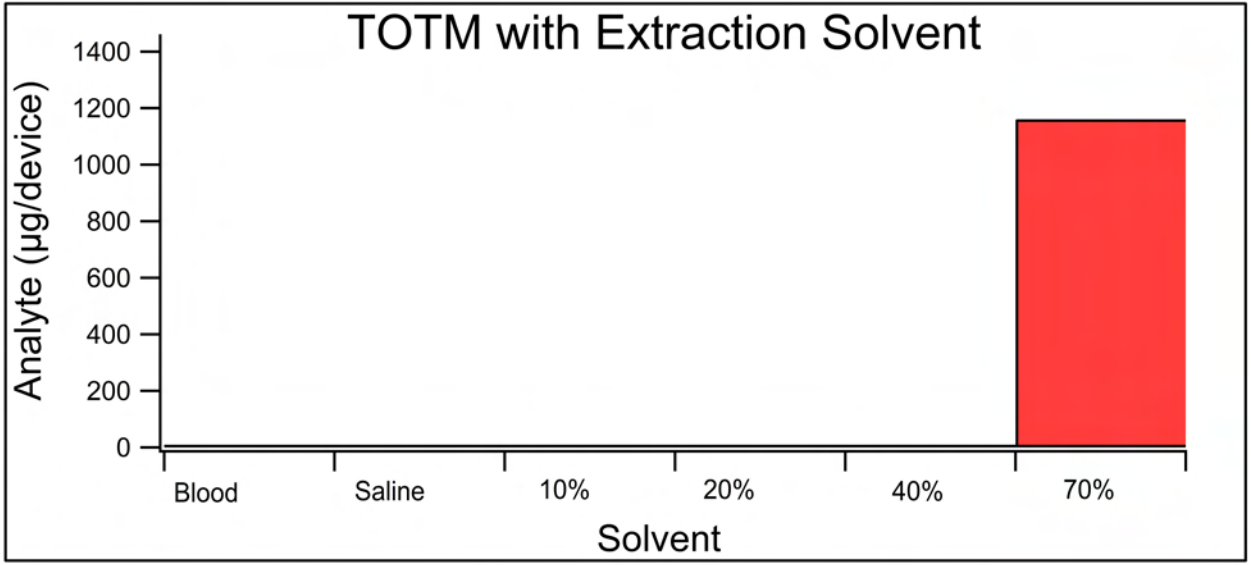

MDA with Extraction Solvent
DMA (µg/device)
100
80
60
40
20
0
Blood
Saline
10%
20%
40%
70%
Solvent

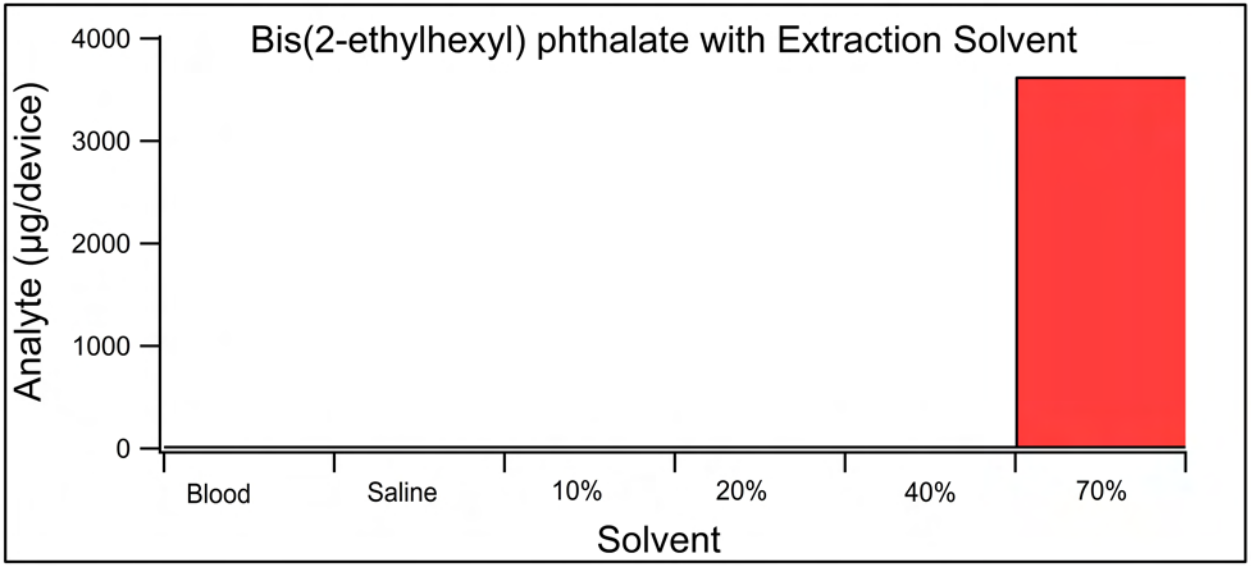

Myristic Acid with Extraction Solvent
Myristic Acid (µg/device)
140
120
100
80
60
40
20
0
Blood
Saline
10%
20%
40%
70%
Solvent

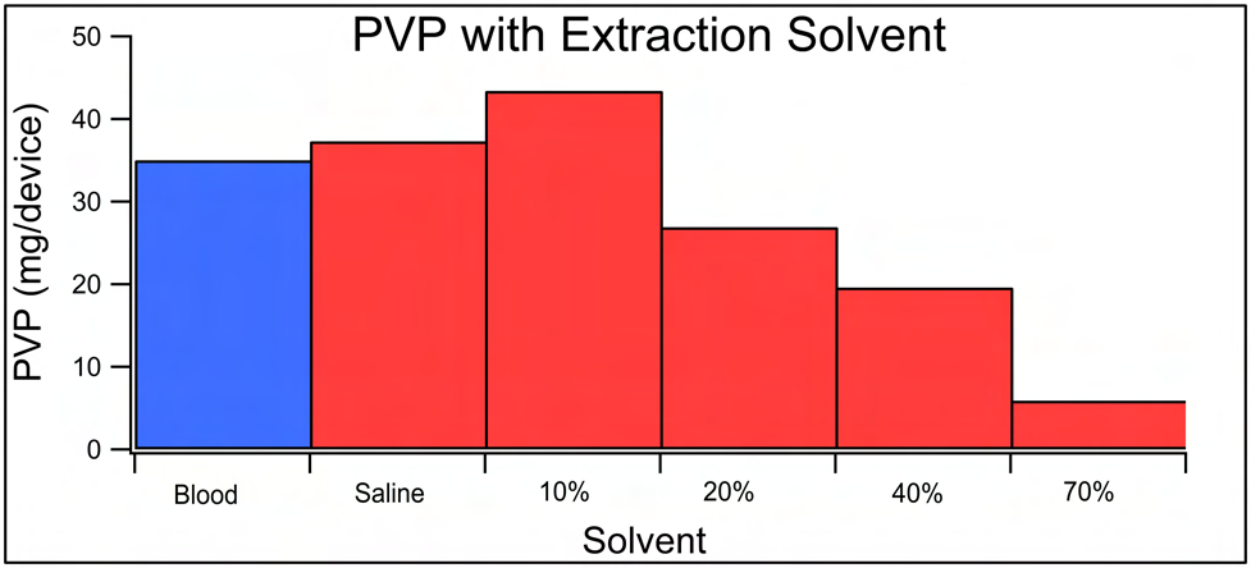

BPA with Extraction Solvent
BPA (µg/device)
60
50
40
30
20
10
0
Blood
Saline
10%
20%
40%
70%
Solvent


ME-BPA with Extraction Solvent
ME-BPA (µg/device)
10
8
6
4
2
0
Blood
Saline
10%
20%
40%
70%
Solvent


DME-BPA with Extraction Solvent
DME-BPA (µg/device)
300
250
200
150
100
50
0
Blood
Saline
10%
20%
40%
70%
Solvent


TOTM with Extraction Solvent
Analyte (µg/device)
1400
1200
1000
800
600
400
200
0
Blood
Saline
10%
20%
40%
70%
Solvent


Bis(2-ethylhexyl) phthalate with Extraction Solvent
Analyte (µg/device)
4000
3000
2000
1000
0
Blood
Saline
10%
20%
40%
70%
Solvent


PVP with Extraction Solvent
PVP (mg/device)
50
40
30
20
10
0
Blood
Saline
10%
20%
40%
70%
Solvent

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