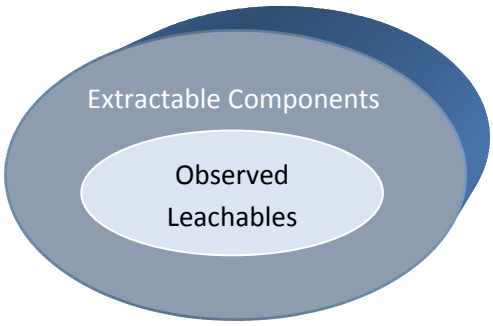
Determining Extractables and Leachables in Polymeric Materials

Overview

The following white paper provides an overview of the process used to determine extractables and leachables from plastics. This is most typically desired for plastics which are utilized in biomedical devices or in food contact applications. The following topics are covered:

- *Definitions*
- *The Purpose of E&L Testing*
- *Why is E&L Testing Important*
- *Regulatory Environment*
- *What are Extractables and Leachables?*
- *How is an E&L Study Conducted?*
- *Sample Selection*
- *Sample Preparation*
- *Extraction Conditions*
- *Identification of E&Ls (Qualitative Analysis)*
- *Determination of E&L Concentration (Quantitative Analysis)*
- *Acceptable Levels for E&Ls*
- *Quality Control in an E&L Study*

Definitions



E&L Study

Extractables and Leachables Study

Leachable

"substances that can be released from a medical device or material during clinical use[1]"

Extractable

"substances that can be released from a medical device or material using extraction solvents and/or extraction conditions that are expected to be at least as aggressive as the conditions of clinical use[1]"

The Purpose of E&L Testing

Nearly twenty percent of the US adult population has an implanted medical device. The use of plastics in medical devices is widespread, encompassing nearly all types of devices. The types of plastics used in these devices include polymers such as polycarbonate, polyurethanes, silicones, polyvinylchloride (PVC) and polyethylene, among others. Plastics contain additional components beyond the base polymer.

These components include a wide variety of plastic additives used to improve polymer properties as well as impurities and byproducts remaining after polymer synthesis. Nearly all polymers contain residual monomer and oligomers (polymer chains <2000 Mw). These small molecules can impart increased toxicity to the material if they are released from the plastic matrix. Extractables and leachables (E&L) testing is used to identify toxic small molecules present in the plastic and to measure their quantity. This data is then used in conjunction with toxicology data for assessing health and safety concerns.

Why is E&L Testing Important?

The importance of E&L testing has been highlighted due in a large part to a number of highly publicized incidents. In 2009, a large product recall was performed for Tylenol Arthritis Pain caplets following complaints related to a moldy smell. This was eventually traced to the leaching of the wood preservative 2,4,6-tribromoanisole which had migrated from wooden pallets into plastic packaging.[10] Other examples included growing concern about components such as Bisphenol A (BPA) from polycarbonate materials used in products for children and Phthalate plasticizers found commonly in PVC. Phthalate plasticizers have been shown to be endocrine-disrupting. The FDA has issued guidance in relation to these chemicals and has limited their use for certain applications.[2,3] A wide range of other extractable components are also under study and some have been found to have deleterious interactions with drugs.[4]

Regulatory Environment

In response to the hazards posed by E&L components, the FDA has provided guidance indicating that E&L testing should be conducted as a part of 510(k) submissions for medical devices. [5, 6, 7] In addition, the "FDA Food Safety Modernization Act" now includes specific reference to E&L components. It states that "A drug or device shall be deemed to be adulterated... if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health.[8] This definition therefore encompasses any small molecule component which could be released from the material and which has toxic effects (extractables). In addition, industry guidance documents have been issued by bodies such as the Product Quality Research Institute (PQRI) providing recommended maximum daily dosage levels for leachable components.

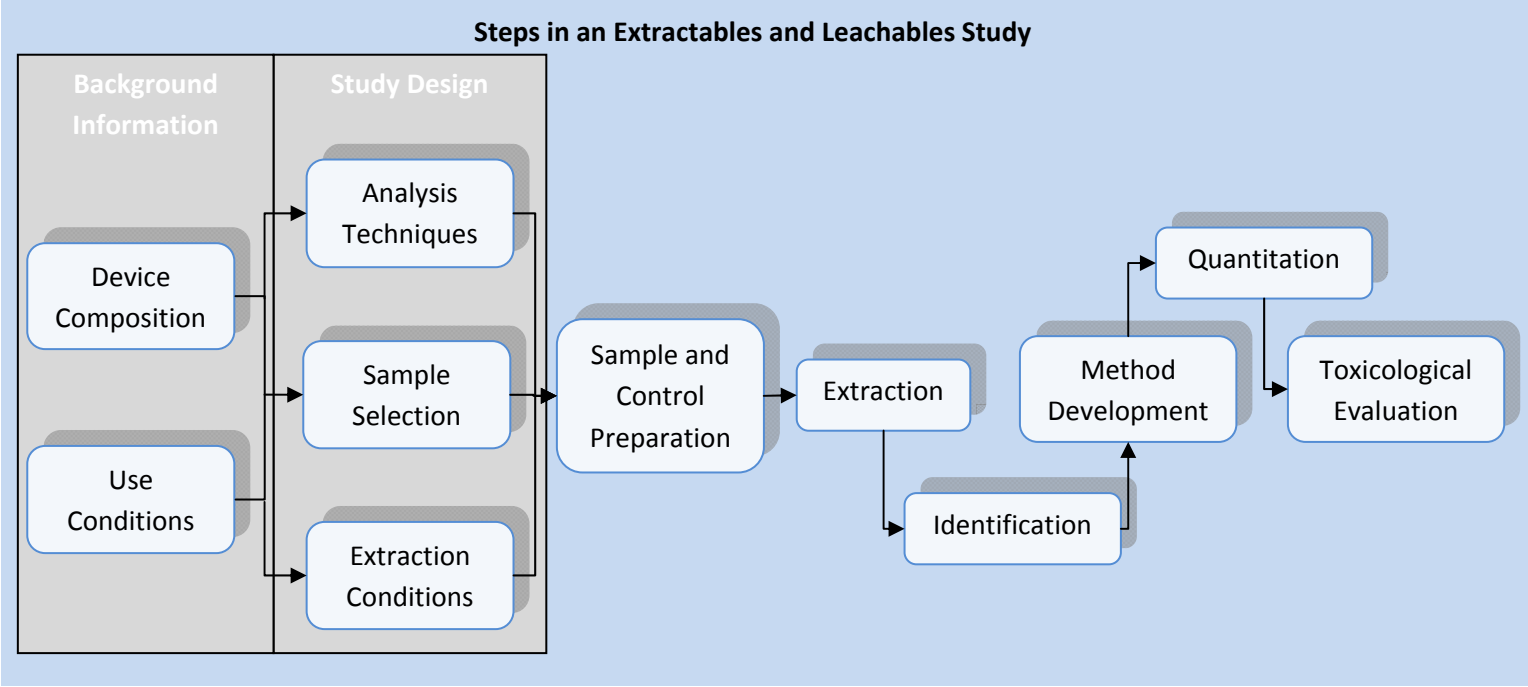
What are Extractables and Leachables?

So what exactly are extractables and leachables chemically? They are the small molecules present in a polymer system including antioxidants, surfactants, slip agents, plasticizers, acid scavengers, cross-linking agents, lubricants, residual monomers and oligomers. It is not uncommon to find tens or even hundreds of individual small molecules species which are extractable from a given polymer system depending on the extraction conditions. Many of these compounds may not be leachables depending on their polarity and the use conditions of the device.

How is an E&L Study Conducted?

Guidance for the proper procedure for performing extractables and leachables studies is provided in ISO 10993-12. Additional information regarding the proper selection of analytical methods for chemical characterization is provided in ISO 10993-18. This series of documents defines the topics which should be considered when performing an E&L study. The primary steps include:

- Sample selection
- Sample preparation
- Extraction
- Qualitative analysis
- Quantitative analysis



Sample Selection

The primary consideration in sample selection is that the specimen be representative of the final product as it will be applied to the patient or food contact application. E&Ls can be created or picked up during the manufacturing process. In order to accurately simulate the risk to the patient it is necessary to utilize samples which contain all of the same E&Ls as can be found in the actual device. For this reason it is preferred that the actual medical device be utilized for testing whenever possible. If sterilization of the device is required then the E&L study should be conducted post sterilization. When it is not practical to use the actual device, it is also acceptable to prepare composite samples but special care must be taken to ensure the sample is representative of the final product. Extraction of individual sample components can also be useful for determination of the source of individual E&Ls.

Sample Preparation

Less sample preparation is generally required when it is possible to test a medical device in its entirety. Analysis of an entire device often involves submerging the device into the extraction solvent or filling the device as appropriate. In this case, sample preparation generally consists of only creating appropriate enclosures to seal off non-wetted regions of the device.

If analysis of the entire device is not practical, then representative portions of the device may be utilized. This generally involves machining or cutting portions of each of the materials used to make up the device. It is preferable to collect the materials from a finished device. This will ensure that the materials experienced all the same manufacturing conditions. Care must be taken to ensure that each material present in the medical device is included in proportion to its quantity in the device. Emphasis should be placed on those components which are known to have a biological response. It is generally recommended that plastics be cut into portions with dimensions of 10mm x 50mm or smaller to improve extraction efficiency.

Extraction Conditions

Selection of the optimum extraction conditions depends upon a good understanding of the conditions under which the device will be used. The guiding principle when selecting the extraction conditions is that the extraction should provide an appropriate exaggeration of the expected conditions of product use. This provides a margin of safety when assessing the leachables which can be expected to come from a device. Three different types of extractions are typically applied and are described in ISO-10993-12:

Simulated-use Extraction

An extraction conducted using a method that simulates the expected use conditions.

Exaggerated Extraction

An extraction which uses conditions which are expected to cause a greater amount of extractable material to be released than using the simulated use extraction.

Exhaustive Extraction

An extraction which is repeated until the total amount of extractables is less than 10% of the amount obtained during the initial extraction.

In most cases, a simulated extraction and either an exaggerated or exhaustive extraction will be performed. The simulated use extracts are analyzed to determine what can reasonably be expected to leach from the sample under actual use conditions. The exhaustive or exaggerated extract is used to estimate the maximum amount of extractable material which could extract from the sample under worst case conditions. Exhaustive extractions require that multiple extractions be performed on a single

sample. This can be accomplished either using a traditional extraction approach and applying multiple cycles or using Soxhlet extraction. In either case, verification of extraction completeness is required.

The extraction process is affected by a range of factors including solvent type, time, temperature, agitation conditions and surface-area-to-volume ratio. The optimum conditions are a function of the type of extraction which is desired, the nature of the sample and the analytical techniques which will be used to determine the chemistry of the extracted materials. The intended use conditions for the device must also be considered.

Extractions must be conducted in both a polar and a non-polar solvent. Typical polar solvents include water or saline and typical non-polar solvents include chloroform and hexane. In general, the solvent should be selected to maximize the amount of extractables without dissolving the polymer itself. The volatility of the solvent should also be considered as it is generally desired to concentrate the extracted components to maximize method sensitivity. The extraction solvents must be compatible with the analytical methods being used to identify the extracted components. It is also important that the extraction conditions do not result in changes in the sample chemistry. The sample solution should be agitated throughout the extraction.

The volume of extraction solvent utilized can be determined using either the surface area of the component being extracted or on a mass basis. Generally, the surface area approach is preferred and a surface area to volume ratio of 3 cm^2/ml is applied for most samples. Higher volumes may be appropriate for high surface area materials (sheets, films).

The extraction temperature depends on the intended use conditions and are selected to provide an appropriate exaggeration of the expected use conditions. One of four temperatures is typically applied.

- (37 ± 1) °C for (72 ± 2) h
- (50 ± 2) °C for (72 ± 2) h
- (70 ± 2) °C for (24 ± 2) h
- (121 ± 2) °C for (1 ± 0,1) h

Once an extract is prepared, it is recommended that it be analyzed as soon as is reasonable. If the extract is stored longer than 24 hours, then the stability and homogeneity of the extract must be considered. Concentration of the extract prior to analysis is often necessary to increase method sensitivity. The concentration step should be considered carefully as analyte loss can occur for unstable or volatile components during concentration.

Identification of E&Ls (Qualitative Analysis)

Once an extract has been obtained, it is necessary to use appropriate analytical techniques to identify the chemistry of the components which were extracted. It is beneficial to begin this process by conducting a review of the materials used to make the device to determine the expected starting

materials and additives which are likely to be present. Targeted analyses and confirmation of the applicability of analytical methods and methodologies can then be conducted.

Types of Unknowns

The analytical techniques and the methodologies used are very important to the success of an E&L study. If test methods selected do not have sufficient scope, then successfully extracted components will go undetected. Many device manufacturers are unaware of the limitations of analytical techniques and believe that a single technique can adequately identify unknowns in an extract. Unknowns fall into several broad classes including volatiles, semi-volatile and non-volatile components. In addition, extracted components can be inorganic, such as salts or metals, or organic, such as monomers and additives. In general, the following analytical methods are typically applied for determining the various classes of unknowns:

Organic Unknowns

Volatile

Gas Chromatography Mass Spectroscopy (GCMS), Headspace GCMS (H-GCMS), Dynamic Headspace GCMS (D-HMS), Desorption Mass Spectroscopy (DMS)

Semi-Volatile

Gas Chromatography Mass Spectroscopy (GCMS), Liquid Chromatography Mass Spectroscopy (LCMS), Desorption Mass Spectroscopy (DMS)

Non-Volatile

Pyrolysis Mass Spectroscopy (PYMS), Nuclear Magnetic Resonance (NMR), Fourier Transform Infrared Spectroscopy (FTIR), Gel Permeation Chromatography (GPC)

Inorganic Unknowns

Metals

Inductively Coupled Mass Spectroscopy (ICP-MS), X-ray Fluorescence (XRF)

Salts

Ion Exchange Chromatography (IEC), Inductively Coupled Mass Spectroscopy (ICP-MS)

Other methods may also be applied for targeted analyses of expected components.

While the use of proper analytical techniques is essential, this is only a starting point for a successful study. Proper identification of unknowns is dependent upon interpretation of the data obtained to

confirm the chemistry of each unknown. If a compound is not commercially available, it may not be possible to obtain a definitive identification without a great amount of analytical effort. The accuracy of unknown identification is based largely on the skill of the analyst and involves a combination of manual data interpretation, the use of spectral and compound database searches and an understanding of how different methods can be used to confirm one another. The quality of the analytical information can also vary significantly based on the analysis conditions, the analyst's knowledge of the chemistry of the materials (background information), and the exact instrument type and suitability. These factors place a high importance on the choice of the laboratory utilized to conduct the analyses.

Determination of E&L Concentration (Quantitative Analysis)

To assess the potential hazards associated with leachables, it is necessary to determine the concentration released from the plastic. This is often very challenging due to the large variety of extractables and leachables as well as the requirement for proper identification. In addition, identification beyond obtaining a molecular formula may not be feasible if the components are not commercially available. This is especially true in cases where the material is a degradant or reaction byproduct from the polymer synthesis. For these reasons, several different strategies must be applied for quantitation of components identified in an E&L study.

In our experience, two primary methods are applied for quantitation. They are formal quantitation using standards of known concentration and semi-quantitation using a surrogate standard.

Formal Quantitation

This method of quantitation is performed by preparing a calibration curve using standards of the compound of interested prepared at different levels which bracket the concentration observed in the extract. This method is the most accurate and is preferred for compounds which are known to be of special concern (high toxicity) as this method is more accurate than semi-quantitation. It requires that a commercially available standard can be obtained.

Semi-Quantitation

This method utilizes a standard with a similar chemistry as compared to the unknown and is most appropriate when no commercially available standard exists. The accuracy of this method depends on the similarity of the instrument response for the surrogate standard as compared with that of the target analyte. This is often difficult to verify experimentally and is instead assumed. For this reason, the use of semi-quantitation is less desirable.

Acceptable Levels for E&Ls

The acceptable level of the leachables is compound dependent and is evaluated with the aid of a toxicologist. A guidance document has been issued by the Product Quality Research Institute (PQRI), an independent consortium from industry, academia and the FDA, for extractables and leachables for orally

inhaled and nasal drug products. In it they defined a safety concern threshold (SCT) of 0.15 ug/day for inhalation products.[9] This can then be converted to an Analytical Evaluation Threshold (AET) for comparison with the value determined during an E&L analysis. The European Medicines Agency (EMA) uses the same quantity as their target threshold. Other sources recommend using a limit of 1.5 ug/day.[11, 12]

Quality Control in an E&L Study

The accuracy and reliability of an E&L study should be confirmed using rigorous quality control measures. This includes some or all of the topics discussed below depending upon the quality system requirements for an individual E&L study:

Analysis Blanks

It is typical for all solvents and reaction vessels to provide some level of background. The blank is utilized to confirm the source of these components and to demonstrate that they do not arise from the sample. The analysis blank is a control sample which has undergone all of the same steps which have been utilized for the samples but which contains only the pure extraction solvent. It is very important that the blank be placed into the same type of extraction vessel and that it be exposed to the same conditions as the samples. Consideration should also be given to any enclosures which may contribute to the background of the analysis.

Negative Control

In addition to the analysis blank, other negative controls such as an instrument blank or a known reference material may be utilized to confirm cleanliness of the analytical system. These controls can be used to establish that the systems utilized for the analysis are free of extractable components and to demonstrate that a component did not arise from the sample. The most commonly used negative control is the instrument blank which demonstrates that the analytical system is free of extraneous peaks.

Positive Controls or Spiking Study

It is important to verify the performance of the analytical method at the time of the analysis. A positive control is any reference material which when analyzed demonstrates that the method is performing to expectations. One type of positive control utilizes a spiking study. The spiking experiment gauges method accuracy by adding a known quantity of the compound of interest to the extract solution and demonstrating that an acceptable recovery is obtained. In order to perform a spiking experiment, it is required that a commercially available standard exists. Spiking studies are especially valuable during E&L testing due to the large number and variety of components which must be quantified. This puts an increased burden on the analytical methods to be more generic and thus many of the compounds under study have not been previously quantified in the

matrix of interest. The spiking study provides an effective means of verifying method accuracy for the component of interest.

Validation of Analytical Methods

Method validation is a process whereby the performance characteristics of a method are verified and it is confirmed that the method is suitable for the intended purpose. Analytical methods should be validated as appropriate with respect to parameters such as accuracy, linearity, limit of detection, limit of quantitation, specificity, range, ruggedness and system suitability. Many of these parameters apply to quantitative methods as these parameters can only be verified when a particular compound is under study. Validation of qualitative methods is generally more generic and utilizes a set of example compounds to demonstrate the methods suitability for a breadth of analytes.

Conclusion

Performing an E&L study is an important part of verifying the safety of a medical product. Design of an E&L study requires an understanding of the materials used to construct the device and the expected use conditions. E&L studies are best conducted using an analytical strategy which is informed by expectations of potential extractables and which has sufficient breadth for discovery of unexpected components. The laboratory which conducts the study must have sufficient expertise in unknown identification to properly leverage information from multiple techniques, databases and control experiments to allow for positive unknown identification. They must also have the breadth of instrumentation which allows for analysis of a wide range of potential analytes. Finally, they must also be experts at analytical method development such that they can utilize this knowledge to develop quantitative methods for the components identified. Jordi Labs specializes in the analysis of plastics and has the experience and knowledge to make your E&L study a success. Jordi partners with our customers to develop and execute E&L studies empowered by over 30 years of analytical experience and state of the art instrumentation.

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