Extractables and Leachables: What to do and why to do it?

Roger Pearson, PhD., Aspen Research Corporation, Maple Grove, MN 55369

Abstract

The studies used to determine **what** chemicals (and how much of them) can "move" in some way from a source material (usually polymeric in nature) to another sink (food, pharmaceutical, the body, the air) falls into the general category of what is termed "extractables" and "leachables" studies. The reasons the studies are done are to meet regulatory guidelines and to aid risk professionals (toxicologists) in assessing a given products safety. In practice, it is the **analytical methods** used to detect, identify, and quantify the chemicals that migrate out of the base material that poses the most significant obstacle in helping risk assessors make a determination as to the risk posed by a given product.

Introduction

The effort to understand what chemicals might move from a packaging into a pharmaceutical or from a medical device into the body is driven by both regulatory concerns and process concerns.[2,3] The regulatory concern focuses around the potential harm that might occur due to exposure to chemicals. To that end, chemical migration studies are done on both drug packaging and medical devices that attempt to assess what compounds may move from the drug package into the drug (which is then the route of human exposure), or, in the case of a medical device, move from the device directly to the body via some route depending on the nature of the device.

In the case of the medical community, these migration studies have been termed "extractables" and "leachables" (E&L) studies. There are differences in the approaches and goals of the two types of studies that are often misunderstood and, even when understood, open to much debate.

The goals of this paper are to demonstrate how the two types of studies differ and to discuss what types of analytical instrumentation and techniques are used to achieve the goals of the studies: the determination of **what** chemical entities are extracted and leached under the conditions of the study, and, at times, the determination of the **amounts** that are extracted or leached.

Extractables Studies

The primary purpose of an extractables study is to determine what chemicals are present in a given material and what is the total burden of that chemical contained in the material. Such data, once obtained, can be used by a risk professional to determine if a potential risk exists if all the available chemical leached out. Extractable studies (or results of them) are often requested by end users of the base polymers and there is more pressure being applied to material suppliers to conduct these studies.

The design of the extractables study should include extraction of the base material in suitable solvents of different polarity so that a thorough extraction of the polymeric (or other) matrix is achieved. In the end, the choice of solvents and extraction conditions will need to be agreed upon by all stake holders and should be justifiable to any regulatory body to which the data may be presented. Commonly used extraction solvents include DI water, 10% ethanol/water, isopropanol, dichloromethane, hexane, and water adjusted to low and high pH. In addition to the choice of solvents, the extraction conditions of time and temperature need to be investigated so that it can be demonstrated that the extraction was complete. This is usually accomplished by either conducting the extractions over increased time periods at a given temperature until the concentration of a chemical in the extract is the same (comes to steady state) with increase time, or by sequential extractions until the n^{th} extraction yields a concentration that is 10% or less of the initial extraction (Figure 1.)

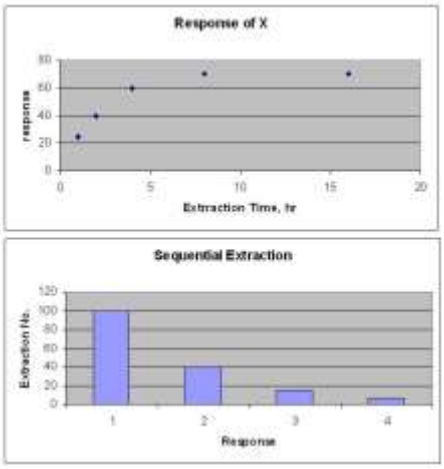

Figure 1. Effect of extraction time (top panel) or sequential extraction (bottom panel) on extracted compound response.

For organic chemicals, most of the concern for risk analysis focuses on compounds with molecular weight less than 1000. Thus it is not necessary to completely dissolve the polymer, only to swell it. For metals analysis, it is often easier to simply digest the sample and then analyze

for metals which gives a good indication of what the total metals burden (maximum potential exposure) is. A caveat to the extractables study is the potential loss of very volatile compounds from solvent extractions during the analytical work up prior to analysis. Many times the solvents used in the extractions have to be volume reduced, or back extracted into an organic solvent and then volume reduced, prior to analyzing by chromatography techniques. When this is done, very volatile compounds can be lost. For this reason, it is often recommended in extractables studies that a thermal extraction be done for residual solvents.

After the extractions are completed, what is critical is the choice of analytical tools used to detect chemicals which might have been extracted. That will be discussed that after addressing the leachables study design.

Leachables Studies

Leachables studies fall into two categories and are usually conducted by the producer of the drug or device. The first applies directly to pharmaceuticals where the drug solution itself can be analyzed during storage stability studies. Often times the information gained in extractables studies can be used to help tailor the leachables studies as information as to what chemicals to look for would exist from the extractables study. This is important because it helps the analyst craft the drug extraction method (not always a simple task) to a compound of concern.

The second type of leachables studies goes more towards estimating what might leach into a system that is not readily extractable, such as the human body. Like the extractables study, a range of solvents need to be used that are reasonable surrogates for the leachables sink, but the conditions of extraction (or leaching) are generally not as aggressive as those used in the extractable studies. The point of the leachables study is not to find out what the maximum possible leaching might be, but to try and assess what might truly occur under real use conditions. Most often solvents such as 0.9% saline or phosphate buffered saline (PBS) as used along with a slightly modified solvent such as 10% ethanolic water (or saline). Generally the studies are set up to do the extractions at 37 ˚C (body temperature) for medical devices with extraction times varying depending on device use. These times can be quite long (months) if the device is an implantable and quite short if the device is in short contact (hours).

The choice to conduct leachables studies for non pharmaceuticals is usually made only if the extractable studies indicate a potential risk and is often times more limited in its targets of chemicals, usually targeting only those that are suspect based on the extractables data. It also holds true that the analytical methods used in leachables studies are more defined and the methods are often validated to GMP guidelines prior to undertaking the studies.

There may be occasions (and actually there are many) where a company may choose to skip the extractables study and only conduct a leachables study for target compounds that they know have been purposely added to a product formulation that has been well characterized previously.

Analytical tools and E&L

In either type of study, at the end of the extractions, one is left with a solution that may have chemical compounds, metals, or inorganic compounds that have been in the original product and been extracted. The challenge is to find the correct analytical techniques, with appropriate sensitivities, that can detect, identify, and be used ultimately to quantify the amounts of the compounds. As an added problem, the concentrations of concern are usually quite low, on the order of single parts per million (based on the product weight) or so. Generally, the compounds that are extractable and of concern result from the processing chain (Figure 2).

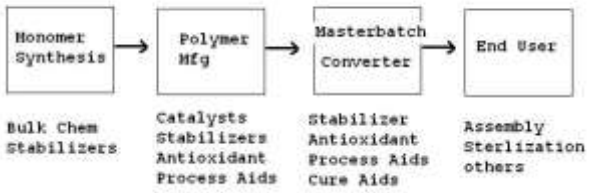

Figure 2. Process chain where additives occur

Because of the diverse nature of many of the additives, and thus potential extractives, both knowledge of the process and knowledge of the analytical techniques that are amenable to detecting the additives are needed. For instance, many of the antioxidants that are used cannot be detected by gas chromatography (GC). So if one were to do the extractions and only analyze the resultant extract by GC, an antioxidant could well be present but would never be detected. Or, if a metal residual from a catalyst was extracted, that too would not be detected by GC. So the choice of instruments to use to analyze the resultant extracts is critical. It probably holds that no one laboratory has all the possible analytical instrumentation that could possibly be needed. At a minimum, we suggest the extracts be analyzed as outlined in Table 1.

Analytical technique	**Detects**
Headspace GC/MS	Very volatile compounds
GC/MS	Volatile to semivolatile compounds
HPLC/UV-MS	Semivolatile and polar

	compounds
ICP/AES	Elemental (metals and others)
FTIR	Polymeric residuals and others
Ion Chromatography	Anions and cations

Table 1. Analytical tools for analysis of extractables and leachables

Another problem exists after the extraction solvents have been analyzed by the various techniques. That is, if something is detected, how does one go about identifying what the unknown is? The identification of the elemental signature is fairly straight forward using ICP, but not the valence state. The problem exists more for the organic compounds which is the reason for the mass spectrometric detection coupled to the GC and HPLC. The mass spectral databases for electron impact GC/MS are quite large and complete and many detected peaks can be identified (at least tentatively) by match of unknown mass spectrums to compound known mass spectrums. The HPLC/MS spectral matching power is not nearly as robust. The technique is more recent than GC, and the mass spectrometer can be operated in any of 4 modes. But it does afford more information than any other type of detector used coupled to an HPLC

Once the extraction solutions have been analyzed, along with the identification problem, there also exists the problem of deciding what the response on any one of the techniques means as regards risk. Does one try and identify every peak detected? If guidance exists, or if one accepts an allowable exposure value (5 ug per day), then it is possible to back calculate what analytical response is reasonably similar to such an intake [4]. Generally some generic mix of compounds of known concentrations at or just below the concentration equivalent to the allowable is analyzed and used to set the response above which unknown compounds would attempt to be identified (Figure 3). In Figure 3, one can see that a number of compounds are detected, but there are only about 10 to 12 where effort would be expended in trying to identify and quantify them because they are the only ones with response near or above a level of concern.

This approach is quite useful, but is predicated on the fact that all stakeholders can agree upon an analytical threshold level of concern.

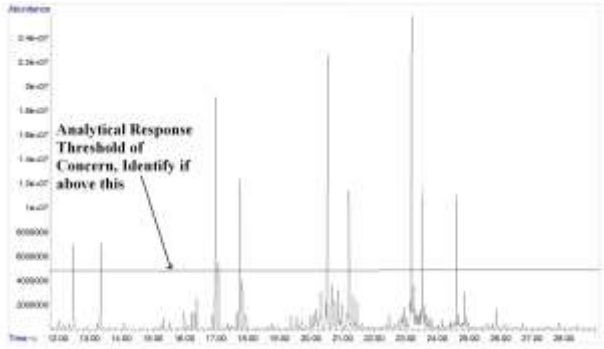

Figure 3. GC/MS chromatogram showing the response above which compound identification would be attempted

Of course, there are a few compounds that have known high risk factors that would require special attention (DEHP, BPA, MDI) and to which the general threshold would not apply.

After all the data from all the instrumental analytical techniques has been pooled, there are a number of outcomes based on the types of studies. Supplier generated extractable studies can be used by the end product developer to correlate to leachables studies that the product developer will have to do. If both extractables and leachables studies have been conducted, the data should exist to help identify the source of a particular compound in a leachables extract. In addition, the methods developed during the course of an extractable study can be optimized and validated for the more important submission data contained in leachables studies.

Conclusions

E&L studies are extremely valuable and often required by regulatory agencies. The understanding of the information that is gleaned from each, and how it is used is imperative if the studies are to yield the desired out comes. The analytical task is not trivial, and requires laboratories equipped with instrumentation capable of analyzing for a wide variety of chemicals at trace levels. This means that the laboratory analysts must be experienced in analyzing for trace level contaminants. In addition, because there are few if any prescriptive tests, the establishment of the study design is critical and requires a laboratory capable of analyzing non routine samples.

References

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Key Words: Extractables and Leachables, trace analysis, pharmaceuticals, medical device.