

EXTRACTABLES AND LEACHABLES TESTING OF POLYMER DEVICE COMPONENTS

Keith Scott

Rapra Technology, Shawbury, Shrewsbury, Shropshire, SY4 4NR, UK
Tel: +44 (0) 1939 250383 – fax: +44 (0) 1939 251118 – email: kscott@rapra.net

BIOGRAPHICAL NOTE

Keith Scott joined Rapra Technology in 1982. After some years involvement in the development of liquid polymer curing systems and environmental aspects of polymer chemistry (e.g. nitrosamine formation) he joined the Polymer Analysis Team at Rapra in 1995. From 2000 until 2006, he had responsibility for day-to-day operations, as Business Manager of the Polymer Analysis Team. Keith has become increasingly involved in managing various projects for the medical and pharmaceutical sector and at the start of 2007 became the Technical Manager of the Pharmaceutical Solutions Team at Rapra Technology which specialises in providing analytical solutions to this sector with particular emphasis on Extractables and Leachables testing of polymers.

ABSTRACT

This paper discusses the application of chemical analysis techniques to the study of extractables and leachables. These can arise from either medical devices or drug delivery devices or their polymeric components. Best Practice guidelines (PQRI) for inhalation drug delivery devices is discussed along with a standard (ISO 10993-18) dealing with chemical characterisation of materials used in medical devices.

1. INTRODUCTION

The examination of extractables and leachables from medical products and devices is growing in importance. This has arisen from ISO 10993 Standard Biological Evaluation of Medical Devices – Part 18 Chemical Characterisation of Materials and also from various guidelines produced by the FDA^{1,2}. These guidelines are concerned with various drug delivery devices, such as meter dose inhalers (MDI) and dry powder inhalers (DPI), and cover a wide range of aspects including extractables and leachables from rubber and plastic components in these devices.

In recent years the PQRI^a Leachables and Extractables Working Group has submitted best practice guidelines³ for Extractables and Leachables Testing to the PQRI Drug Product Technical Committee and the U.S. Food and Drug Administration. These guidelines have made an important contribution to Extractables and Leachables Testing of Orally Inhaled and Nasal Drug Products (OINDP).

This paper discusses the importance of Extractables and Leachables testing to Medical and Drug Delivery Devices, firstly considering the testing of inhalation drug delivery devices (OINDP) and then medical devices.

2. EXTRACTABLES AND LEACHABLES TESTING OF OINDP

The assessment of Extractables and Leachables in OINDP, as recommended by the PQRI, has three main parts:

1. Extractables
2. Leachables
3. Routine Extraction Testing

Each of these stages is guided by various safety thresholds.

^a Product Quality Research Institute

2.1. Safety Thresholds

The PQRI Leachables and Extractables Working Group have recommended two safety evaluation thresholds which have been justified from a toxicological or safety perspective:

- A Safety Concern Threshold (SCT) of 0.15 µg per day, which is defined as the threshold below which an individual leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects;
- A Qualification Threshold (QT) of 5 µg per day, which is defined as the threshold below which a given leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity relationship (SAR) concerns

These thresholds represent absolute exposures, expressed as total daily intake per day. They need to be converted into relative amounts expressed as an amount of a particular leachable per drug product or extractable per mass of component. This threshold is known as the Analytical Evaluation Threshold (AET). The AET is determined by consideration of the SCT and the specific drug product configuration (e.g. total number of doses in the Drug Product, number of doses per day, mass of individual components).

For an extractables from a device component the AET (µg/g) can be determined using Equation 1:

$$AET = \frac{SCT \cdot D_t}{D_d \cdot m} \dots\dots\dots \text{Equation 1}$$

- D_d - Doses per day
- D_t - Total Labelled doses
- m - mass of component

The AET (µg/device) for a drug delivery device (e.g. an MDI) can be determined from Equation 2:

$$AET = \frac{SCT \cdot D_t}{D_d} \dots\dots\dots \text{Equation 2}$$

- D_d - Doses per day
- D_t - Total Labelled doses

The AET is also affected by the experimental uncertainty of the analytical methods used to identify and quantify the individual extractables/leachables. The Final AET (AET_{Fin}) is derived the Estimated AET (of Equations 1 and 2) and the analytical uncertainty of the analytical methods. Where an extractable is quantified by comparison with the specific authentic reference compound, the Final AET is equal to the Estimated AET. However it is recognised that during CES it is not practical to accurately quantitate each and every individual extractable with an authentic reference compound and so the Final AET is used to rationalise the overall scope of these studies.

In order to determine the Final AET, an assessment of the average response factor for a given technique and the analytical uncertainty in this average response factor needs to be made. This is done by taking a range of authentic reference materials and determining their individual response factors (from suitable five point calibration series'). The average response factor (Rf_{av}) is then determined along with the relative standard deviation ($Rf_{\%RSD}$). The Final AET is then calculated as indicated in Equation 2.

$$AET_{Fin} = AET_{Est} \left(1 - \left(\frac{Rf_{\%RSD}}{100} \right) \right) \dots\dots\dots \text{Equation 3}$$

Alternatively the Final AET can be taken as half the Estimated AET.

The extractables which cannot be quantified against their specific authentic reference standard are quantified using the average response factor (Rf_{av}).

This approach works fairly well for GC-MS data, however it not so reliable for LC-MS data. Care should be taken when applying average response factors and the associated relative standard deviations to LC-MS data.

2.2. Controlled Extraction Study (CES)

A CES is a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of an OINDP. The CES and its results can be used to:

1. Establish a basis for the development and validation of routine quality control methods and acceptance criteria for critical component extractables profiles (Routine Extractables Testing).
2. Establish a basis for the development and validation of leachables methods suitable for use in drug product leachables studies.
3. Allow for the "correlation" of extractables and leachables profiles.

Controlled Extraction Studies should be carried out on all the critical components of the OINDP. The PQRI Leachables and Extractables Working Group have made the following recommendations regarding Controlled Extraction Studies.

Controlled Extraction Studies should:

- Employ vigorous extraction with multiple solvents of varying polarity
- Incorporate multiple extraction techniques
- Employ multiple analytical techniques
- Include a defined and systematic process for identification of individual extractables.
- Optimise extraction methods
- Should be guided by AET
- Consider the potential for the presence of polycyclic aromatic hydrocarbons, N-nitrosamines and 2-mercaptobenzothiozole (MBT). If their presence cannot be ruled out, these should be considered as "special case" compounds requiring specific analytical techniques and technology defined thresholds.

The controlled extraction study has to parts:

1. Qualitative
2. Quantitative

2.2.1. Qualitative Controlled Extraction

Initially a qualitative extraction study is carried out on the components. There are three main phases to the extraction process:

1. Vigorous extraction using multiple techniques and solvents
2. Analysis of the extracts using multiple techniques
3. Assessment of data.

2.2.1.1. Extraction with Multiple Solvents and Techniques

Typically the components are extracted in three different solvents of varying polarity. The solvents used will depend on the drug product, for example:

MDI:	dichloromethane (to mimic propellants), propan-2-ol and n-heptane
DPI:	water, propan-2-ol and n-heptane
Spray Products and Nasal Sprays:	water, propan-2-ol and n-heptane

Typically three extraction techniques are employed:

1. Reflux extraction
2. Soxhlet extraction
3. Ambient Temperature with ultrasonic agitation

For DPI components it is recognised that migration of chemical entities through the vapour phase may occur. To address this possibility, headspace methods can also be used in the assessment of DPI components.

2.2.1.2. Analysis of Extracts

There is no single analytical technique that could cover the identification of all potential extractables. Although there are specific analytical methods for particular additives, incorporating all these methods into a study such as this is neither practical nor necessary. Therefore, a number of generic methods are used, which are able to detect and identify a very broad range of polymer additives. A list of these techniques with target species is included in Table 1.

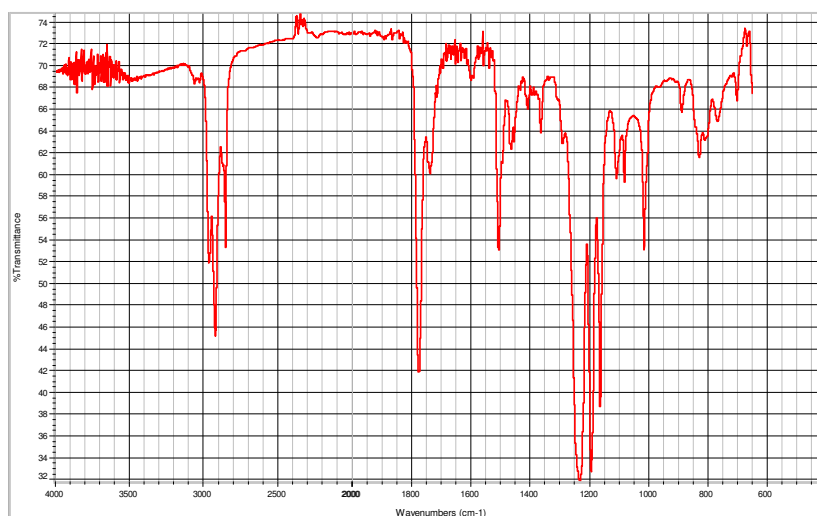
Table 1

Analytical Method	Target Species
Gas Chromatography - Mass Spectrometry (GC-MS)	Low molecular weight monomers, initiators, antioxidants, UV absorbers, lubricants, process aids, plasticisers, anti-static agents, modifiers and oligomers.
Headspace Gas Chromatography Mass Spectrometry (GC-MS) (DPI components only)	Very volatile species including monomers, initiators, solvents and other low molecular weight species.
Liquid Chromatography - Mass Spectrometry (LC-MS).	Medium to high molecular weight polar species including antioxidants, UV absorbers, plasticisers, lubricants process aids, heat stabilisers.
Gravimetric and Fourier Transform Infrared Spectroscopy (FTIR)	High molecular weight species fillers mineral oil lubricants, plasticisers, silicone oil mould release agents and oligomeric material.
Acid digestion Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES)	Metal compounds. Catalysts, stabilisers etc. (Screening analysis, of the component as received, for 36 elements, is carried out in the qualitative phase of the CES.)

2.2.1.3. Data Assessment

The gravimetric and infrared analysis of the extract provides a generic quantification and identification of major portion of the extract. This is often comprised of oligomeric material derived from the polymer. Figure 1 shows the infrared spectrum of a heptane extract of a polycarbonate component. This clearly shows that the extract mainly consists of oligomeric material.

Figure 1: Infrared Spectrum of a Heptane Extract of a Polycarbonate Component



Individual components of the extract are separated by chromatographic techniques to enable qualitative and quantitative analysis. Gas chromatography is applicable to the components of high to medium volatility and liquid chromatography to components of low volatility. Both chromatographic techniques employ mass spectral detectors, although the detectors for the two techniques are different in character. UV detection is also used in-line with the MS detector for liquid chromatography. Figure 2 and Figure 3 show typical GC-MS and LC-MS chromatograms for extracts of two different components.

Figure 2: GC-MS Chromatogram of a Heptane Extract of a Polystyrene Component

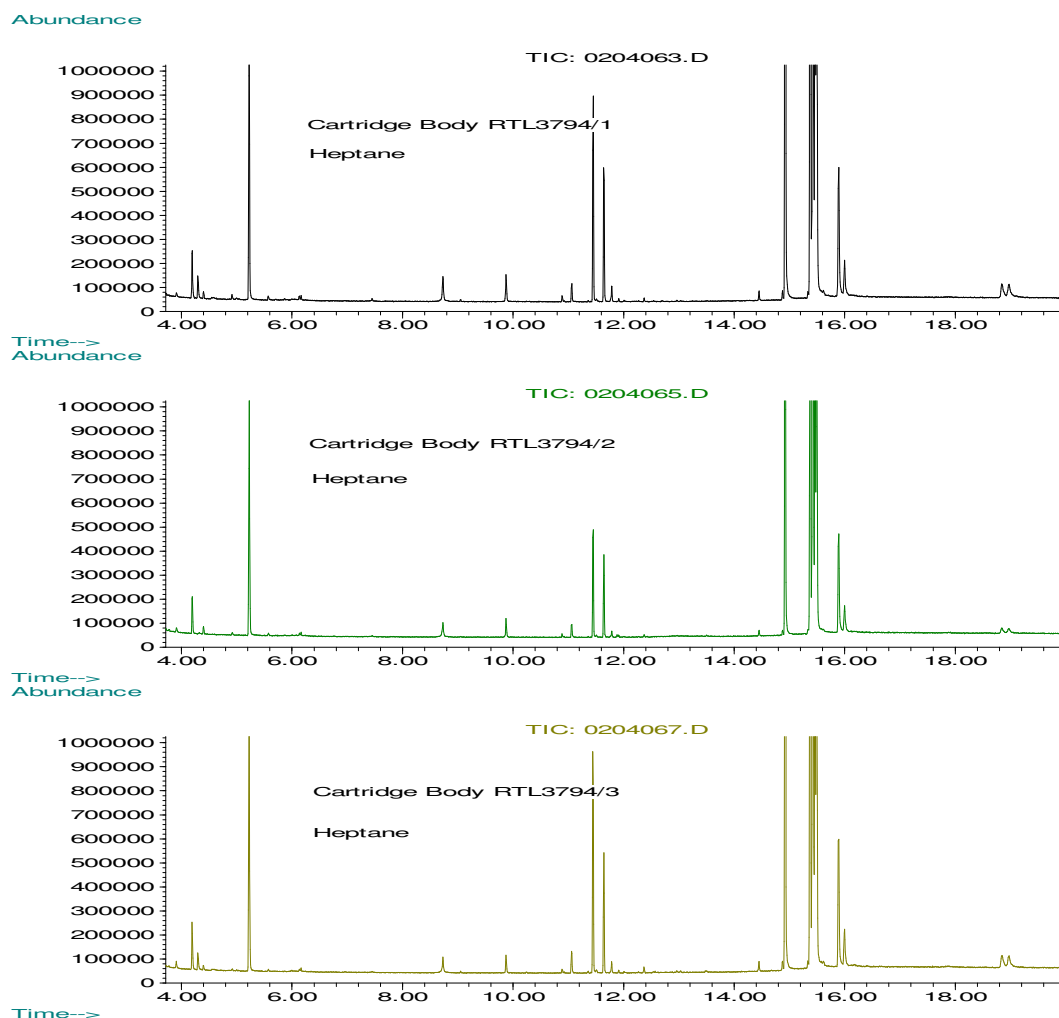
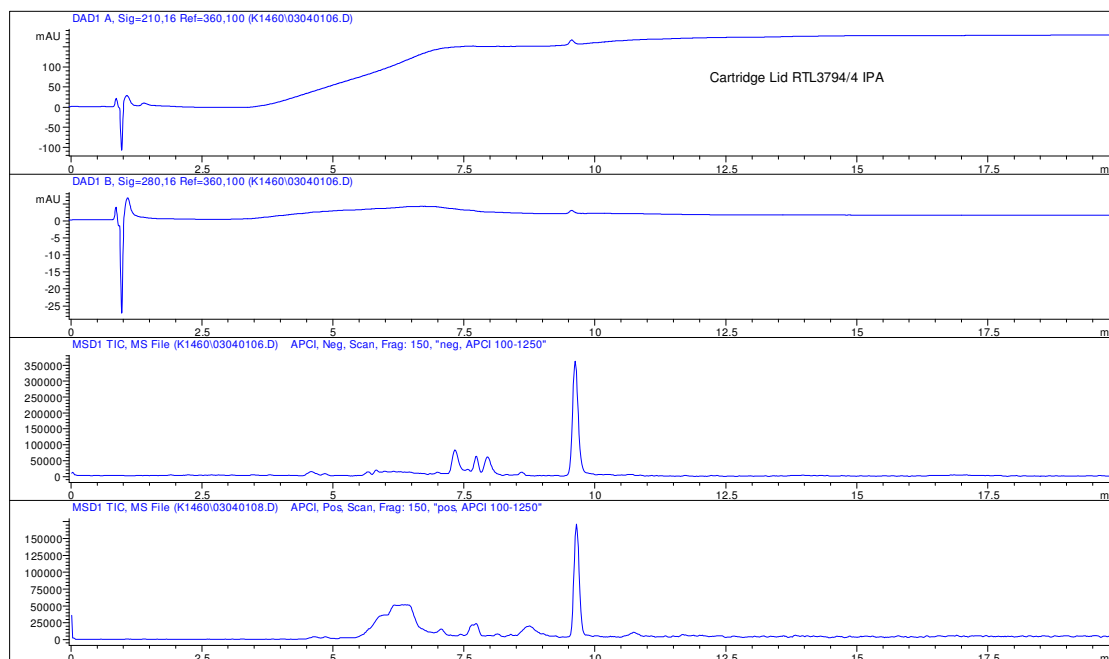


Figure 3: LC-MS Chromatograms (UV, APCI +ve & -ve) of Propan-2-ol Extract of a Polypropylene Component

The best practice guidelines state that the data and processes used to identify individual extractables should be clearly defined and understood. The identification categories shown in Table 2 are assigned to each of the chromatographic peaks considered. Depending on the identification categories applicable, and other factors, the assignment of an individual extractables can be characterised as confirmed, confident or tentative. Table 3 provides guidance as to how assignments may be characterised.

Table 2 Identification Categories

Identification Category	Typical Identification Data
A	Mass spectrometric fragmentation behaviour
B	Confirmation of molecular weight
C	Confirmation of elemental composition
D	Mass spectrum matches automated library or library spectrum
E	Mass spectrum and chromatographic retention index match authentic reference sample

Table 3: Characterisation of Assignments

Assignment	Identification Categories/Other Factors
Confirmed	A, B (or C), and D (or E)
Confident	Sufficient data to preclude all but the most closely related structures
Tentative	Data has been obtained that are consistent with a class of molecule only.

At the level of the Qualification Threshold, complete identification of an extractable or leachable should be possible. Where such identification is not possible an explanation should be provided. Extractables present below the AET need not be identified.

2.2.2. Quantitative CES

The findings of the Qualitative CES are used to select "definitive" extraction techniques. These techniques are defined by the solvent and extraction method (reflux, Soxhlet etc). These methods then require optimisation and verification. The best practice guidelines state that 'while complete validation is not recommended or expected for Controlled Extraction Study methods, it is recommended that appropriate experiments be accomplished to verify that quantitative results are accurate and precise'.

2.2.2.1. Optimisation

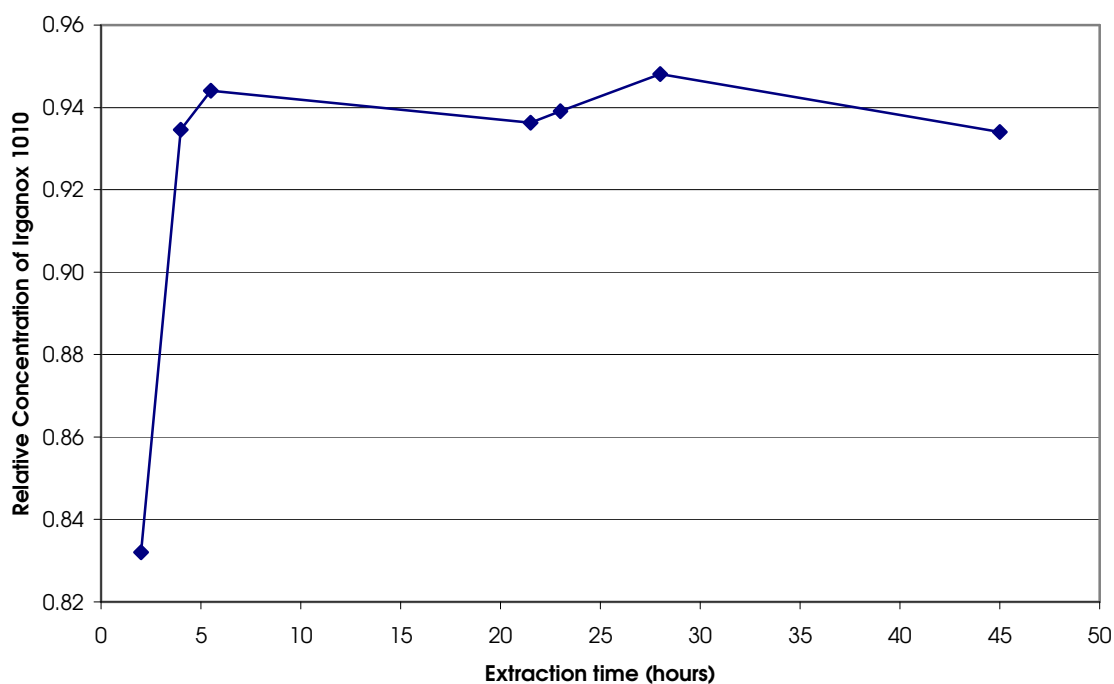
An optimised extraction method is defined as one that yields a high number and concentration of extractables, and achieves steady-state (*i.e.* "asymptotic") levels. Consideration of Jenke's directives⁴ should also be made. These state:

1. Extraction techniques/methods used for CES should be vigorous, but not so aggressive as to alter the qualitative and/or quantitative nature of the extractables profile, and therefore preclude an extractables/leachables correlation.
2. Extraction techniques/methods used for CES must be technically justified and optimised to produce extractables profiles at least equivalent to leachables profiles obtained under worst case conditions of drug product use, allowing both qualitative and quantitative extractables/leachables correlations.

Optimisation may be achieved by extracting the component in a solvent containing a suitable internal standard. At various time intervals aliquots of the sample extract are taken and analysed to determine if asymptotic levels of extractables can be achieved.

Figure 4 shows that for a polypropylene component, 5 hours refluxing in heptane was required to extract asymptotic levels of the antioxidant Irganox 1010.

Figure 4: Optimisation of Reflux Extraction of a Polypropylene Component in Heptane. Irganox 1010 Concentrations Based on LC-UV Analysis



2.2.2.2. Precision, Accuracy and Linearity

The precision of the extraction can be assessed by carrying out multiple extractions of a given component. The quantities of the more abundant extractables are determined and repeatability assessed.

Accuracy can be assessed by carrying out the extraction process in the absence of the component but with known quantities of target analytes being added to the extraction solvent. After the extraction experiment the levels of the target analytes are determined and compared with the expected amounts.

The linearity of the response for each of the reference compounds can be determined from a calibration series.

2.2.2.3. Extraction of Components

The component is extracted using the verified extraction conditions and the extracts will be analysed to identify and quantify the extractables. Where appropriate (*i.e.* LC-MS and GC-MS), quantifications can be made using an external calibration of the authentic reference compounds. Where authentic reference compounds are not available, estimates of the levels present can be made by reference to the average of the response factor of a suitable range of reference compounds.

Analysis by LC-MS, GC-MS, ICP-AES, gravimetric and infrared spectroscopy is appropriate.

2.3. Leachables Study

In these studies the drug product is stored under various controlled conditions and analysed for leachables at multiple time-points over the anticipated shelf-life of the product.

The following points should be addressed in Leachables Studies:

- Analytical methods, based on those used in the CES, should be developed for quantifying leachables in the drug formulation. These methods should be validated.
- Analytical Evaluation Threshold
- A comprehensive correlation between extractables and leachables profiles.
- The potential for the presence of "special case" compounds should be considered.

2.3.1. Stability Storage

The OINDP should be stored under controlled conditions and the Drug Formulation analysed for leachables at multiple time points over the anticipated shelf-life of the product.

The orientation of the stored products should represent a worst case scenario. For example MDIs should be stored in the inverted orientation. However other orientations may be used in addition to this worst case scenario.

Suitable storage conditions for storage (ICH Q1A(R2)⁵) and suggested time points for analysis are given in Table 4.

Table 4: Storage Conditions and Suggested Time Points for Leachables Analysis

Condition	Temperature (°C)	Relative Humidity (%RH)	Time Points (months)
Long Term ¹	25 ± 2	60 ± 5	0, 6, 12, 24, 36
	30 ± 2	65 ± 5	
Intermediate	30 ± 2	65 ± 5	0, 6, 12, 24, 36
Accelerated	40 ± 2	75 ± 5	0, 3, 6, 9, 12

¹ Either set of conditions can be used for Long Term Storage

2.3.2. Time Point Analysis

2.3.2.1. Leachables Analysis Method Development and Validation

Analytical methods for analysing the drug formulation should be developed. These methods should be based on those used during the Controlled Extraction Study (CES) of the critical components which come into direct contact with the drug formulation during storage.

Whilst the developed methods should be capable of quantifying the relevant extractables identified in the CES, they should also be able to identify the presence of other leachables that may be present drug formulation.

Target detection and quantification limits of the methods should be governed by the AET.

Once developed these methods should be validated.

2.3.2.2. Extractable and Leachable Profile Correlation

A qualitative and quantitative correlation between extractables and leachables profiles should be established. The correlation should consider the results of extraction studies on multiple batches of components and leachables studies on multiple batches of drug product over multiple stability storage time-points.

To establish a qualitative correlation between profiles, it must be shown that compounds detected in the leachables study were also present in the Controlled Extraction Studies.

To establish a quantitative correlation between profiles, it must be shown that levels of leachables obtained from leachables studies are generally less than the levels of extractables obtained from quantitative Controlled Extraction Studies.

2.4. Routine Extractables Testing

Routine Extractables testing should be carried out on all critical components of OINDP, either to establish extractables acceptance criteria or release of components.

Routine Extractables Testing should:

- Be performed on critical components using methods based on those used in the CES
- Use validated methods
- Be performed using appropriate specifications and acceptance criteria
- Consider the potential for the presence of "special case" compounds.

If a correlation between the extractables and leachables profiles has been established, Routine Extractables Testing can be used to assure that the levels of leachables found in the drug formulation are acceptable.

3. BIOLOGICAL EVALUATION OF MEDICAL DEVICES – CHEMICAL CHARACTERISATION OF MATERIALS

ISO 10993 Part 1 (Biological Evaluation of Medical Devices – Evaluation and Testing) provides a framework for assessing the biological safety of a medical device. This includes consideration of the chemical and toxicological properties of the materials used in the medical device. ISO 14971 Part 1, which deals with risk management for medical devices, also requires consideration of the chemical nature of the materials.

ISO 10993 Part 18 (Biological Evaluation of Medical Devices – Chemical Characterisation of Materials) discusses strategies for obtaining information about the chemical properties of these materials:

- The chemical composition of the materials;
- The materials of construction
- The potential of the materials to release leachable substances.

Chemical characterisation of the extractables and leachables profile of materials can be used in various ways to establish their suitability for a given application:

- As part of an overall biological safety assessment;
- Determination of the level of a leachable substance of particular concern;
- Establishing equivalence between two materials:
 - A new material to replace a clinically established material
 - A final device to a prototype device;
- Screening new materials for use in a medical device.

The components of a polymeric material (Table 5) used in a medical device can potentially be extracted or leached from the device and so have potential for bio-availability. It is important to establish what these potential leachates are and the likelihood that they will be released during the application of the final device. This can be assessed by conducting extractables testing under suitable conditions which take account of the final application of the device.

Table 5: Potential Components of Polymeric Materials

Antioxidants
Antiozanants
Plasticisers
Process aids
Antistatic agents
UV stabilisers
Curing agents
Fillers
Modifiers

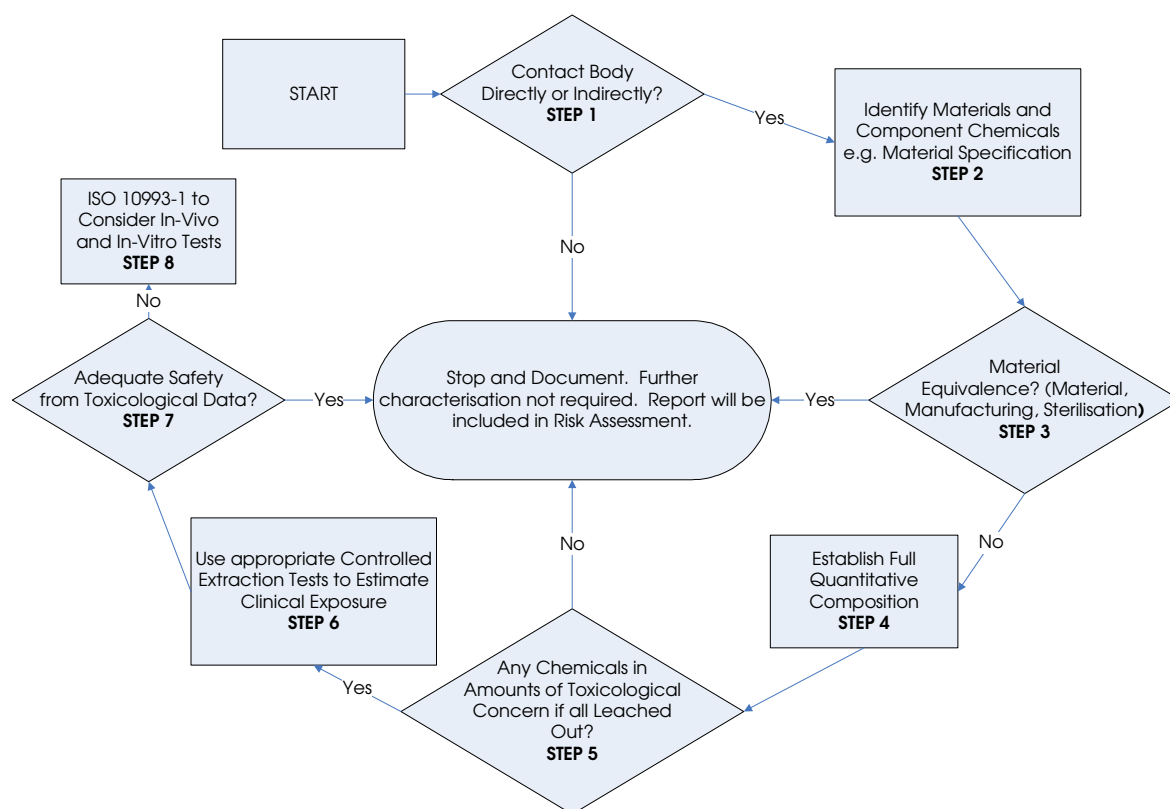
3.1. Strategy

A pragmatic approach to chemical characterisation is to take a number of steps, of increasing complexity, deciding at each step whether further investigation is necessary. Initially it should be established whether the device contacts the body (indirectly or directly) (Figure 5; Step 1).

If body contact does occur then a qualitative assessment of the finished device is required (Figure 5; Step 2). Much of this information may be available from the material suppliers, however if this information is not sufficient then chemical analysis can be used.

It may be that equivalence with an already established material, used in a device with the same clinical exposure, can be demonstrated (Figure 5; Step 3). If this can be demonstrated, either from supplier information or comparative chemical analysis, then further assessment is not required. If this is not the case then the quantitative composition of the material should be determined ((Figure 5; Step 4) and a risk assessment carried out on the basis of this information (Figure 5; Step 5).

The amount of any chemical present still presents a concern then the potential for patient exposure shall be investigated. This is accomplished by carrying out extraction of the device under conditions which simulate the application of the device (Figure 5; Step 6). Again a toxicological assessment of this information is carried out (Figure 5; Step 7) and if concern still remains then the *in-vivo* and *in-vitro* testing of the device should be considered (Figure 5; Step 8).

Figure 5: Stepwise Approach to Generating Chemical Characterisation Data for Risk Assessment

3.2. Analytical Methodology

The following analytical techniques can be applied to establishing the qualitative and quantitative composition of materials used in medical devices, which can be used to establish equivalence between materials or make toxicological risk assessments:

- Physiochemical tests (pH, turbidity, NVR, Heavy Metals etc)
- Fourier transform infrared spectroscopy (FTIR)
- High performance liquid chromatography (HPLC)
- Gas chromatography (GC)
- Mass spectrometry (MS)
- Inductively coupled plasma (ICP)
- Gel permeation chromatography (GPC)
- Differential scanning Calorimetry (DSC)

The following sections provide a summary of some of these techniques and their application in this context.

3.2.1. Infrared Spectroscopy

Infrared spectroscopy can be used to confirm the identity of polymers used in medical devices and can be useful to confirm the identify of some additives. Figure 6 to Figure 8 show infrared spectra of three polymers often used in medical devices. These spectra provide 'finger print' information which can be compared against spectral libraries to confirm polymer type.

Figure 6: Infrared Spectrum of ASA

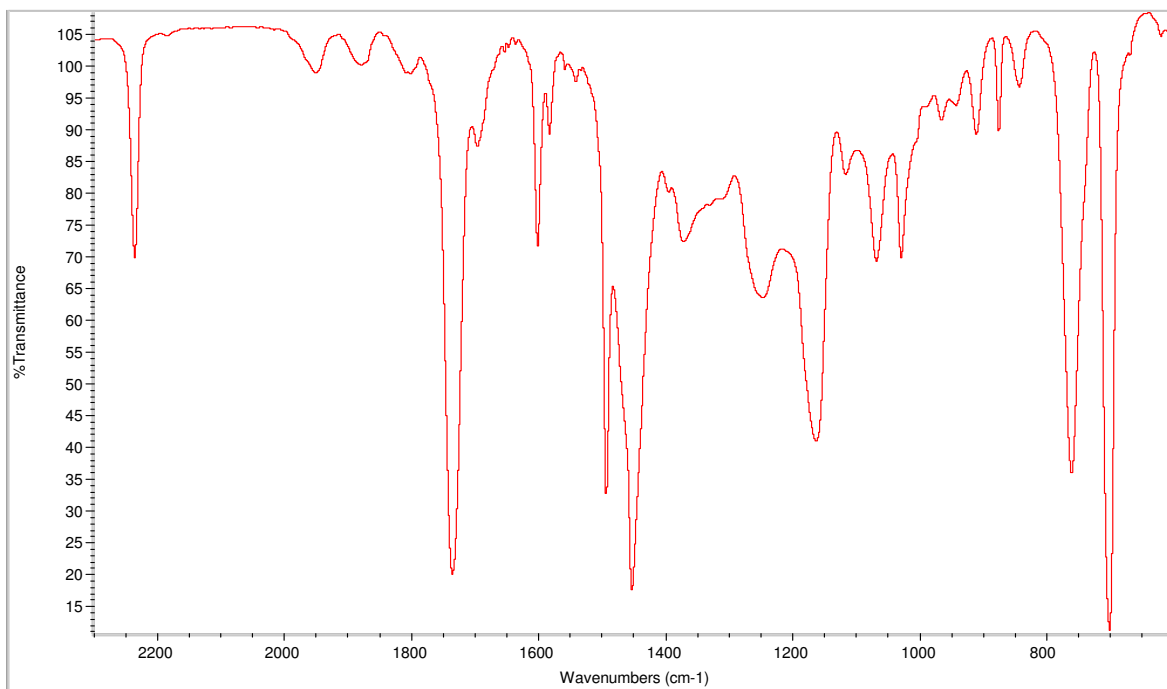


Figure 7: Infrared Spectrum of Polypropylene

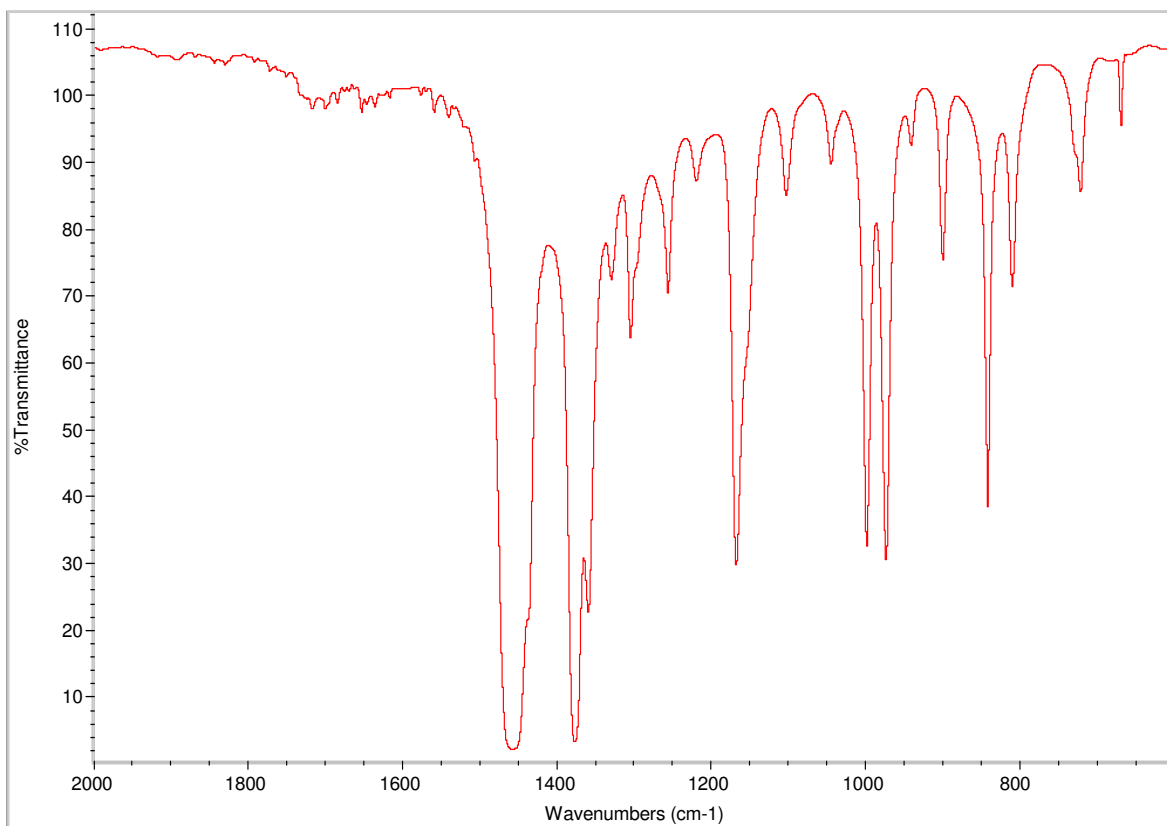
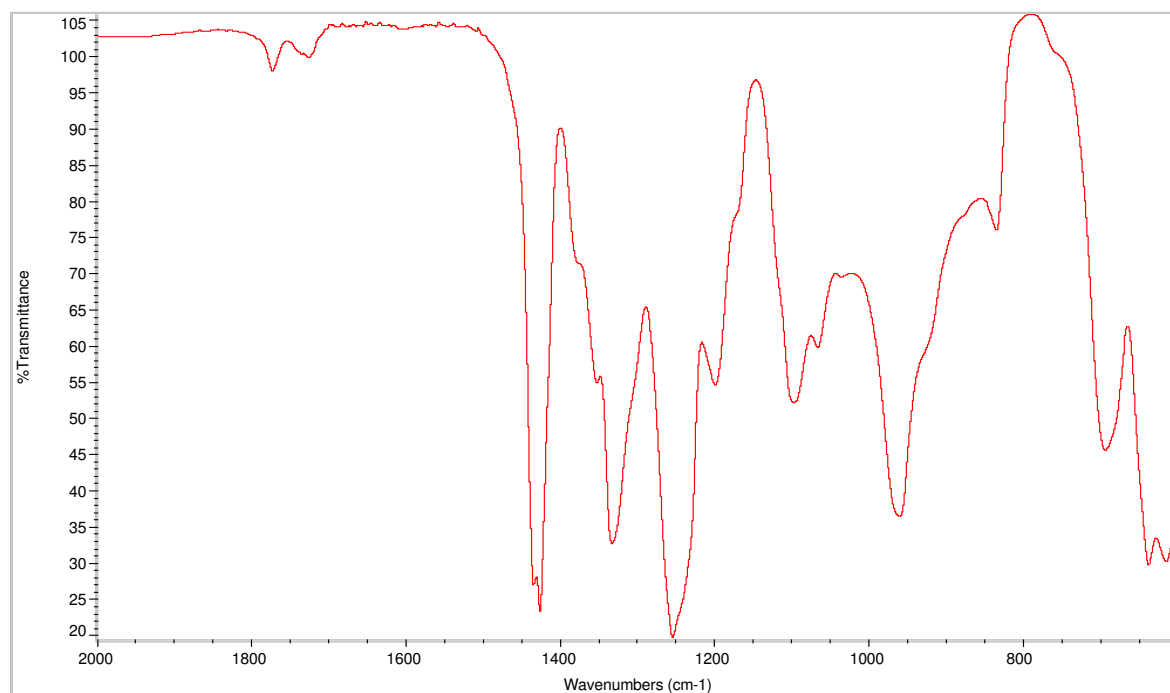


Figure 8: Infrared Spectrum of PVC

3.2.2. Chromatography – Mass Spectroscopy

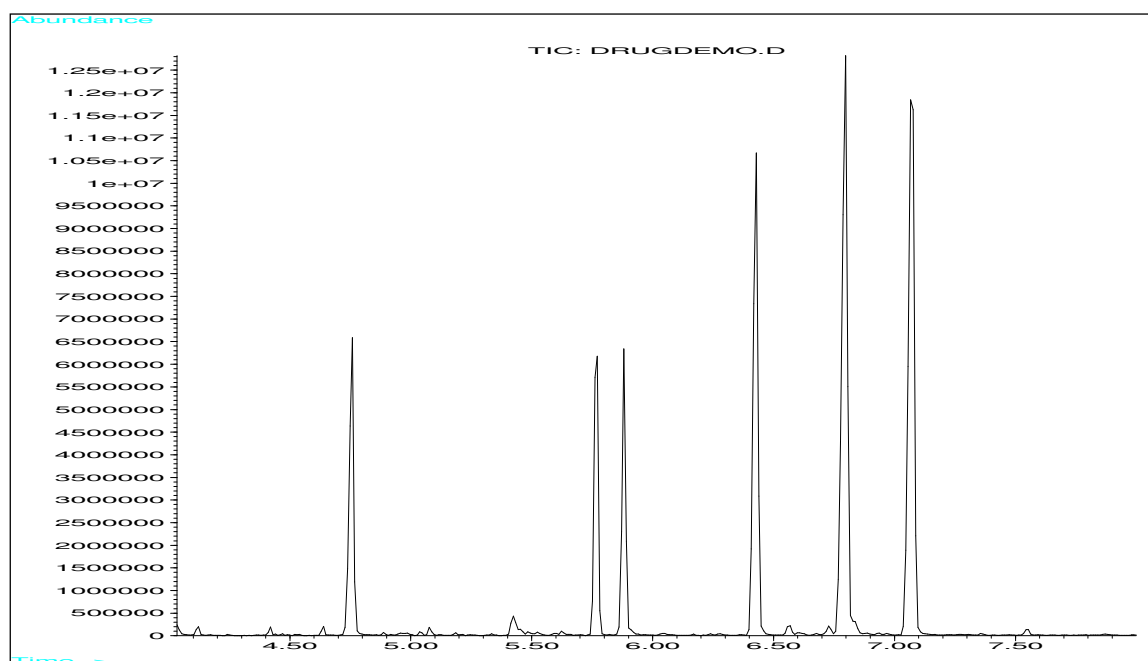
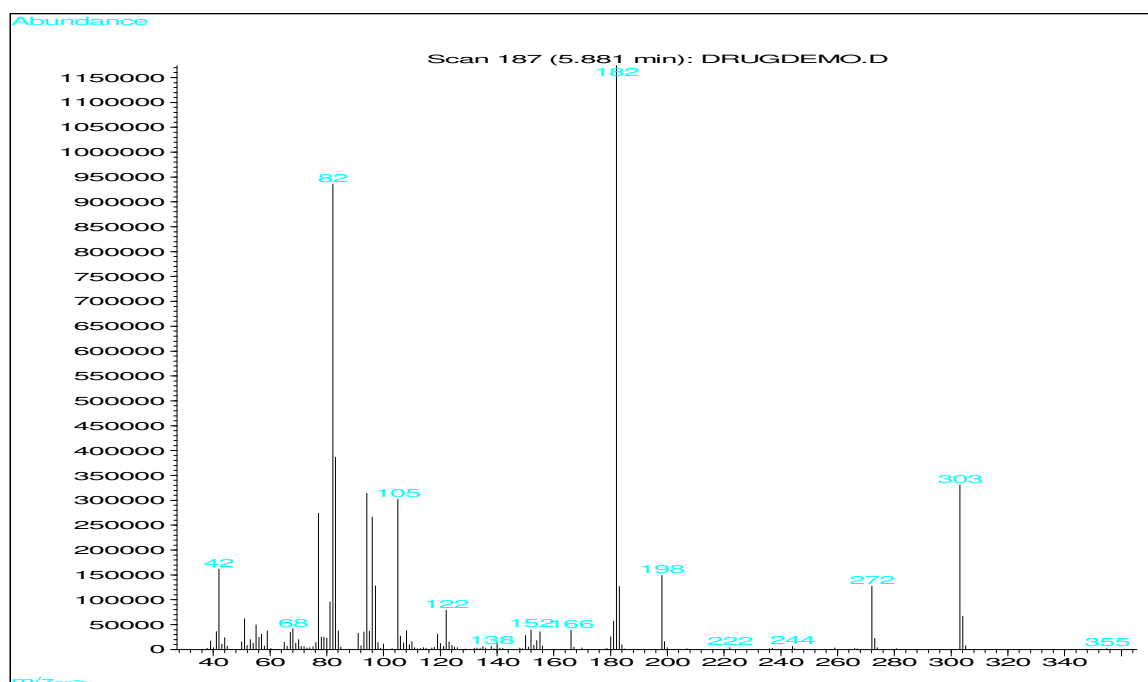
Extracts of polymer materials can be extracted under various conditions. Very vigorous conditions, even dissolution followed by re-precipitation of the polymer, can be used when the composition, either qualitative or quantitative, of the material is required. Less vigorous conditions may be used when clinical exposure is being assessed by extraction in a suitable medium under appropriate conditions.

The extract can then be analysed by either GC-MS (gas chromatography – mass spectroscopy) or LC-MS (liquid chromatograph – MS) to identify and quantify the chemicals present in the extracts.

3.2.2.1. GC-MS

Gas chromatography-mass spectrometry (GC-MS) is used to separate and identify complex organic mixtures. It is applicable to volatile and semi-volatile organic compounds and is a highly sensitive detection technique providing a 'fingerprint' of the unknown analytes.

Figure 9 shows a typical chromatogram which may be generated during the GC-MS analysis of an extract. This shows chromatographic peaks for six separated major components of the extract. For each of these peaks a mass spectrum (see Figure 10 for an example) is available which can be used to identify the component.

Figure 9: Typical Total Ion Chromatogram for GC-MS Analysis**Figure 10: Mass Spectrum of Peak at Retention Time 5.9 Minutes in Figure 9**

3.2.2.2. LC-MS

Liquid chromatography-mass spectrometry (LC-MS) is also used to separate and identify complex organic mixtures but it is applicable to in-volatile organic compounds. Mass spectra are generated however they are different in character to those of GC-MS and are not as useful for the identification of unknowns. However where authentic reference compound are available components of extracts can be identified and quantified.

Figure 11 shows a typical chromatogram generated during the LC analysis of a solution of various antioxidants. Using LC-MS, mass spectra for these antioxidants are generated (for example Figure 12 and Figure 13) which can be used to identify these antioxidants in extracts.

Figure 11: LC-MS Chromatogram of Antioxidant Solution

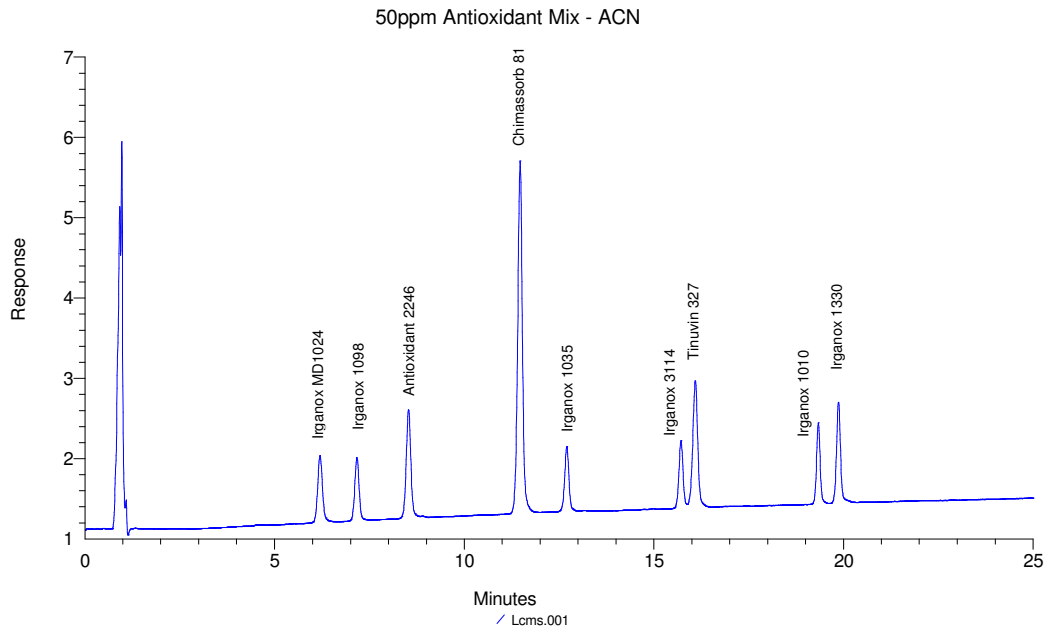


Figure 12: Mass Spectrum of Irganox 1010

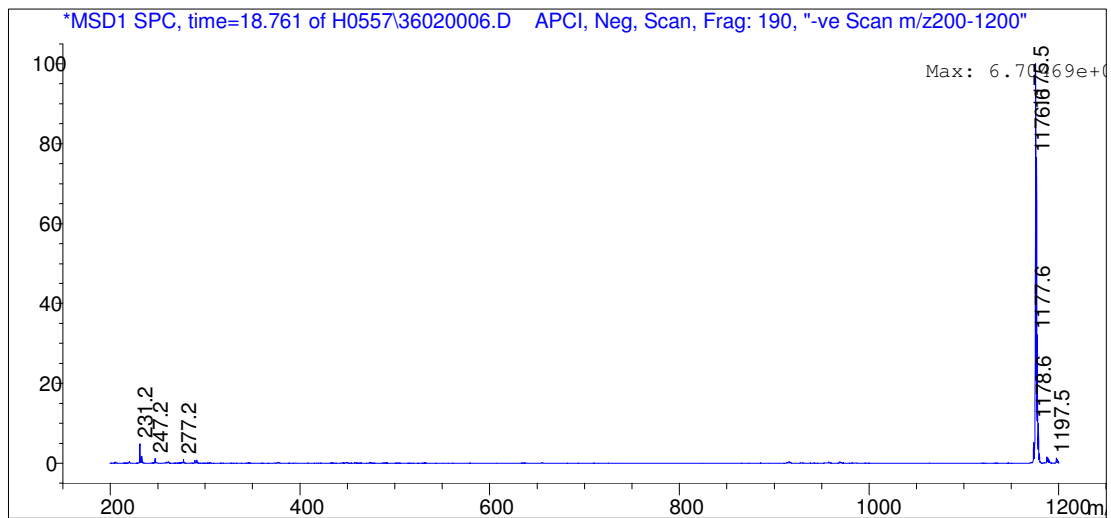
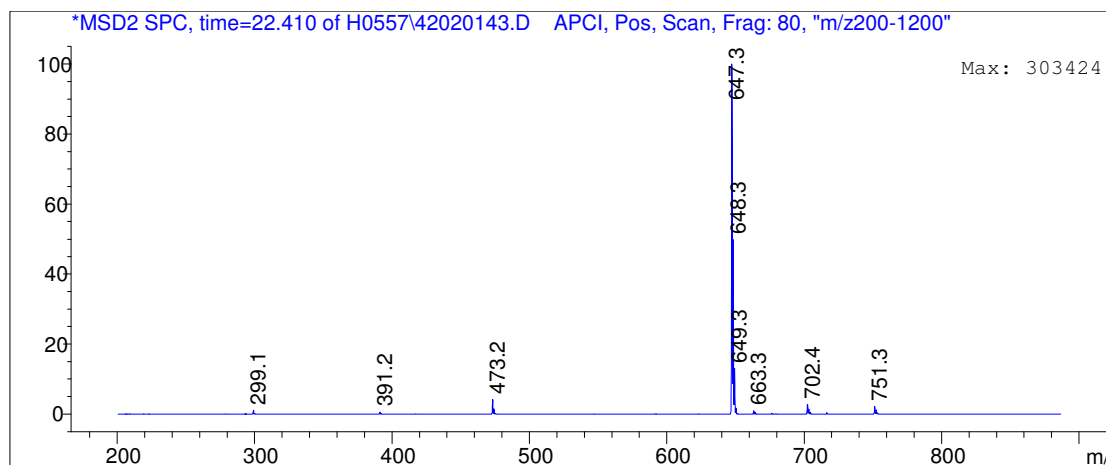


Figure 13: Mass Spectrum of Irganox 168

4. SUMMARY

Chemical analysis is an important tool in the assessment of medical and drug delivery devices. It is particularly useful in establishing what chemicals can be extracted from polymers used in these applications. Some of these extractables may also be leached either into drug formulations (drug delivery devices) or in the patient (medical devices). Chemical analysis can also be used to establish the nature of these leachable components.

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