The Important Role of **Material and Chemical Characterisation** in Device Evaluation

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Parts 18 and 19 of ISO 10993, Biological Evaluation of Medical Devices, currently in draft, are receiving even more emphasis as they become an integral part of the biological safety evaluation of biomaterials and medical devices. An important step in this process is the characterisation of the material and identification of chemicals that can migrate or extract from the polymer components. This article discusses which tests will meet the requirements.

**Source of requirements**

Establishing biocompatibility of medical devices and their materials is of great importance in ensuring product safety. Another important consideration is that the product or material has the necessary properties to perform its proposed function. To evaluate these two fundamentally important issues, it is necessary to perform material and chemical characterisation on the materials. Adverse effects caused by medical device materials are generally chemical effects produced by material components, contaminants or breakdown products that find their way from a device into a patient and cause a biological effect. Figure 1 shows the various types of chemicals that can migrate from polymers.

The biological evaluation of medical devices is governed by ISO 10993 or, in the United States (US), by Food and Drug Administration (FDA) blue book memorandum G95-1, which is a modification of ISO 10993-1. The characterisation of medical device materials is clearly identified by ISO 10993-1 as one of the first steps in their overall biological evaluation.

Because of the importance of materials and chemical characterisation to biological evaluation, draft ISO 10993-18 is being developed as a separate standard on the subject. Part 18 will cover requirements for providing information on the chemical composition of materials and devices, the potential release of leachable substances and the predictive biological characterisation of devices. Part 18 will be issued in 2004. Another standard, ISO 10993-19, which is a working draft titled “Physicochemical, Mechanical, Morphological and Topographical Characterisation of Materials” is in development and will be issued in two to three years. As the name indicates, the standard will address physical...
mechanical and morphological characteristics.

Although it may not seem obvious why chemical and material characterisation is an essential part of biological evaluation, ISO standards clearly link the two together. Understanding the principles presented in ISO 10993-1, draft 10993-18 and draft 10993-19 is imperative and implementing them is an essential part of an overall biological evaluation programme. This article discusses what these ISO standards require and what quantitative and qualitative tests can be used to satisfy the requirements.

The properties to evaluate

Material characterisation is designed to evaluate many different properties of medical device materials. ISO 10993-1 defines six different categories of properties that are to be evaluated. It states in section 4.11 that in the selection of materials to be used in device manufacture, the first consideration should be fitness for purpose having regard to the characteristics and properties of the material, which includes chemical, toxicological, physical, electrical, morphological and mechanical properties. This section of the standard raises two essentially important questions. Is the material safe and does it have the necessary physical and mechanical properties for its proposed function? In other words, is the material biocompatible?

To further emphasise these required tests, ISO 10993-18 states, “consideration of the chemical characterisation of the materials from which a medical device is made is a necessary first step in assessing the biological safety of the device.” Part 18 makes it clear that this testing is necessary and required, but which tests are to be performed is not so clear.

Table 1: Degree of chemical and materials characterisation based on tissue contact and duration.

<table>
<thead>
<tr>
<th>Nature of contact and tissue type</th>
<th>Duration of contact</th>
<th>Types of device</th>
<th>Degree of characterisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface</td>
<td>Limited</td>
<td>Examination gloves, tape, blood-pressure cuff, dental dams, endoscopes</td>
<td>Minimal</td>
</tr>
<tr>
<td>• Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mucous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Membranes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External communication</td>
<td>Prolonged</td>
<td>Dialysis, cardiopulmonary bypass</td>
<td>Intermediate</td>
</tr>
<tr>
<td>• Blood, indirect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant</td>
<td>Permanent</td>
<td>Shunts or grafts, orthopaedic implants</td>
<td>High</td>
</tr>
<tr>
<td>• Blood, direct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tissue contact</td>
<td></td>
<td></td>
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</tbody>
</table>

Figure 2: Infrared analysis provides a rapid, effective means of identifying a polymeric material and of comparing samples to ensure consistency.

To address the two basic issues of safety and function

■ chemical characterisation is required to evaluate potential leachable chemicals and their bioavailability
■ mechanical/physical characterisation will address functionality and safety
■ morphological characterisation will examine the surface of materials in an effort to explain or predict material interaction at the device host interface.

The tests to perform

A variety of techniques are available to perform chemical and materials characterisation. The tests may be performed directly on material samples or on material extracts prepared under specified conditions. These tests, which have evolved over many years, are relevant, sensitive, rapid and inexpensive, and provide extremely valuable information to establish material safety and biocompatibility.

The extent to which a material needs to be characterised depends on the type of material, the end use of the device and the function of the material within the device. The more critical the role of the device and the more important the properties of its materials are to device performance, the more detailed the characterisation programme should be. Table 1 lists the various categories of devices defined in draft ISO 10993-18 and the proposed degree of characterisation necessary.

Prior to performing any of the chemical or physical tests described below, it is extremely important to have precise information on the synthesis of the polymer itself. This information includes:

■ a description of the monomers employed in the polymerisation and solvents used in the synthesis
■ special additives that have been added during production of the material.

For devices with more critical functions or prolonged tissue contact, information on the sterilisation process is important. Knowledge of degradation processes that the device material may encounter in its intended function may be useful in identifying potential degradation products that may be released from the device. If adequate detailed information exists,
the characterisation programme may be conducted partially or solely as a paper exercise.

In the absence of this detail, appropriate analytical techniques must be applied to a material to yield compositional data. Sufficient information must be obtained to identify all toxic hazards arising from the chemical components of the material and sent for risk assessment. When qualitative analysis alone has not provided sufficient data for a toxicological risk analysis to be completed, draft ISO 10993-18 requires quantitative chemical analysis to be performed, documented and then sent for risk assessment. Completion of a characterisation programme requires the close collaboration of analytical chemists and toxicological risk assessors. The chemists provide the necessary qualitative and quantitative data that the risk assessors use to determine device safety. The flow of information between the chemists and the toxicologists is what establishes the process of materials characterisation as an integral part of risk assessment and establishing biocompatibility.

Materials characterisation methods

Infrared (IR) analysis. IR is used extensively to fingerprint materials and should be a part of all characterisation programmes. In this test, IR energy is passed through a thin film of material and the amount of energy absorbed at various wavelengths is measured.3 The result is a chart of wavelength versus absorption that is characteristic of the material (Figure 2). By matching the IR spectrum of an unknown material with that of a known material, proof of identity can be established within the limits of the method.

Thermal analyses. These are useful for fingerprinting materials. In thermal gravimetric analysis, a plot of weight change is made as a function of temperature. In differential thermal analysis and differential scanning calorimetry, an unknown sample and a reference sample are heated at the same rate. In differential thermal analysis and differential scanning calorimetry, an unknown sample and a reference sample are heated at the same rate. In thermal gravimetric analysis, a plot of weight change is made as a function of temperature. Changes in density of a plastic material may herald a change in crystallinity, loss of plasticiser, absorption of solvents, change in porosity and even changes in composition (proportions of resins, pigments or fillers).

Molecular weight. This is one of the most fundamental properties of any molecule. Almost all physical properties of polymers (synthetic or natural) systematically change as the molecular weight is altered. Unlike pure substances of small molecules, polymer samples have a range of molecular weights. For this reason, there is no such quantity as “the molecular weight.” Instead, there are certain average molecular weights or molecular weight distributions (MWD). The most common analytical tool for measuring MWD is gel-permeation chromatography, in which the polymer molecules in a dilute solution are separated according to their hydrodynamic volume when forced through a column of microporous gel particles. Subtle changes in MWD can affect processing properties such as viscosity and cure rates. Mechanical properties such as tensile and impact strength, elastic modulus, hardness and bond strength can also vary with changes in MWD. This analytical tool can be used to qualify incoming resins or device components as part of a materials qualification programme, track lot-to-lot variability and evaluate product stability as part of a stability programme or after radiation exposure.

Physical properties. The significant physical properties of a material can be identified with various test instruments. For example, stress/strain relationships such as tension, compression, shear and flexure are determined with a mechanical testing apparatus. Material hardness is determined by means of a durometer that measures the extent to which the material can be compressed. Surface properties, which are especially important for some specific categories of devices such as those that contact blood can often be observed directly using light, scanning electron and atomic force microscopy.

Extracts characterisation

Some potential extractables from medical device materials are water soluble and others are soluble only in nonpolar environments. For materials that will contact body tissues, extraction activity in both polar and nonpolar environments is relevant. The US Pharmacopoeia (USP) includes physicochemical tests based on water and isopropanol extracts that are particularly useful in defining materials as rich or poor in extractables.7 The tests categorise specific materials extractables in general terms such as nonvolatile residue, residue on ignition, buffering capacity, heavy-metals content, ultraviolet absorption and turbidity. The USP physicochemical tests for total extractables (nonvolatile residue) should be a part of all characterisation programmes regardless of the criticality of the device or its function. The aqueous nonvolatile residue is designed to determine the presence of water-soluble substances without regard to their identity. Figure 3 shows the

![Figure 3: Nonvolatile residue results of aqueous extraction physicochemical testing on polymers commonly used in medical devices. Typically, device materials contain few water-soluble extractables. With reference to this test, USP limits can be used to establish specifications for raw materials.](image-url)
results of aqueous extractions of polymers commonly used in medical devices. Typically, device materials contain few water-soluble extractables and do not exceed the USP limit of 15-mg nonvolatile residue.

Determination of nonaqueous extractables should also be a part of all characterisation programmes. Typically, alcohol (either ethanol or isopropanol) is a more aggressive extraction fluid and most device materials show measurable amounts of nonvolatile residue. Figure 4 shows the results of alcohol extractions of commonly used medical device polymers.

Devices that fall into the more critical category of use require exhaustive extraction followed by analytical methods and instrumentation to identify and quantify extracted chemicals. Gas/liquid and high-performance liquid chromatography are powerful analytical tools that can separate and quantify volatile and semivolatile chemicals. For materials characterisation, these techniques can be used with extracts from, or in some cases solutions of, materials. Chromatography can produce qualitative, fingerprint-like information or, with appropriate standards, can be used to identify and quantify specific chemical components. IR analysis can also be used to fingerprint and identify the chemicals in an extract from a material, and mass spectrometry methods can provide identification of specific molecular structures. Atomic absorption spectrometry can determine the amount of specific metals present in a material or its extract. Inductively coupled plasma spectrometry permits simultaneous determination of all the periodic table elements with a lower limit of detectability in the parts-per-billion range.

Expanding use

Almost all materials to be used in biomedical applications, and consequently nearly every company involved in the medical device industry, will require certain characterisation tests. Material and chemical characterisation forms the basis for understanding the composition of a medical device material and its potential to have an adverse biological effect when the device is put into use. It also serves as a means to ensure standardisation of materials from one lot of devices to the next. As the harmonisation of ISO 10993 standards and FDA requirements proceeds, the methods described above will be used to an increasingly greater extent by the US device industry to aid in the selection of optimal materials and to control the uniformity of medical products. This clearly establishes chemical and materials characterisation as an essential part of medical device biocompatibility.

Case study

A company needed to comprehensively characterise a polymer to be used in the manufacture of an orthopaedic implant. After discussion with technical services personnel, chemical and materials characterisation as described in ISO 10993 was proposed. Good manufacturing practice protocols were written and the following tests performed.

- Purified water, alcohol and hexane extractions performed using US Pharmacopoeia methods (600 cm² surface area to 100 mL of solvent)
- Gas chromatography/mass spectrometry for semivolatile organics of all extracts
- Determination of trace metals/elements using inductively coupled plasma spectrometry
- Gel permeation chromatography to determine molecular weight and low molecular weight species
- Density of material
- Thermal analysis using differential scanning calorimetry or thermal gravimetric analysis
- Infrared scan of the polymer
- Scanning electron microscopy to evaluate surface
- High-performance liquid chromatography for polyolefin additives
- Summary Report and Risk Assessment

By performing these tests, the chemists were able to confirm the identity of the polymer, characterise polar and nonpolar extractables, and determine molecular weight, polydispersity, glass transition temperature and identify polymer additives. The company was able to successfully launch the product.

References

2. General Program Memorandum #G95-1, US FDA, Department of Health and Human Services.
7. USP XXVII, chapters 381 and 661.