MEDICAL ENGINEERING TECHNOLOGIES

TECHNICAL AND SCIENTIFIC SOLUTIONS

Material Analysis in Medical Device Development

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Introduction

I've got a great idea! What we really need is a urethral catheter that slides so smoothly you can't even feel it. It should be totally resistant to bacterial growth, very, very flexible and of course it won't kink. Or maybe we should develop an artificial hip in a material that is so well integrated into the body, that a year after the operation it is indistinguishable from real bone. Ideas are great but what is really involved in getting these great ideas into service?

Medical devices depend upon their physical, chemical and surface properties to deliver their actions and deliver them safely in *vivo.* These properties are dictated, in a large part, by the underlying chemistry of a material. A device developer might go to a polymer (or other material) supplier with a wish list of properties, such as: good biocompatibility, resistance to sterilisation, conformation at body temperature, easy bonding between the polymer and another part of the device made from another material, etc… Or, a newly developed material may have properties that can be applied to medical devices.

Medical device engineers can keep up to date with new materials (for example) by following magazines such as Med-Tech Innovation, or by maintaining links with their local university. Many new materials and devices are developed in conjunction with a research establishment. There are also materials identified independently by these institutions, often with spin off companies being set up to exploit the possibilities. Some materials such as hydroxyapatite used to improve osseointegration[1] of implants have evolved through clinical science. This type of material was first described by Werner[2], who was born in 1786. Similar materials were exploited in dental medicine from the early 1900s and the first documented use of calcium phosphate in human bone repair in 1920[3]. Much academic progress was made in the 1970s[4], with the first use of a HA coating on femoral hip stems in 1985[5]. The research and development of the material in biomedical applications continues apace to this day.

Chemical Analysis

Engineers are mainly interested in the physical properties of a material. A medical device developer has to be interested in other factors as well; the biocompatibility of a material, how it performs during its period of use, how it supports its shelf life and whether there will be any breakdown *in vivo.* Some of these properties can be predicted as a material is developed. For example PEEK[6], was identified as a part of a family of inert rigid materials from its chemical structure. However, often properties must be discovered or at least verified empirically.

Analysis of materials is important during device development and production and all materials should be characterised in their final form. The chemical signature of the material, specified in development, can be used to assure that the future batches of the material or products, from alternative suppliers, are identical. All

additives (including plasticisers, preservatives, impurities, UV protection additives, lubricants, antimicrobials etc.) should be included.

Often it is the surface of a medical device which is of crucial importance. This is where biocompatibility is generally decided, integration with body parts, uptake or release of substances. Even the topology of the surface all have an influence. This is reflected in chemical analysis often being targeted on material surfaces. Much biocompatibility testing is done with extracts obtained by soaking intact devices with a selection of solvents. This process leaches out mobile materials from the surface and it is this leachate that is used in elution Cytotoxicity, along with other biocompatibility tests and in chemical analysis.

A wide variety of chemical analyses are available for the clarification of material structures and components. Listed here are the chemical tests associated with biocompatibility as described in ISO 10993-18:2005 *Biological evaluation of medical devices Part 18: Chemical characterization of materials*. Additional parts of this standard that could be of interest, when performing material analyses, are noted in the references.

Test Methods Described in ISO 10993-18

Abbrev	Analytical Method	Description	Application
DMTA	Dynamic mechanical thermal analysis	Dynamic measurement of stress strain properties, over a range of temperatures.	Characterisation of elastic, rubber and polymeric materials. Of particular interest for devices that behave differently in different phases of use e.g. a polymeric splint, which is heated to conform to patient anatomy and then 'sets' at body temperature.
DSC	Differential scanning calorimetry	Measurement of the heat capacity of a sample by comparing the energy required to change temperature, compared to a reference sample.	Characterisation of polymers, measurement of transitions and phase changes. Characterisation of naturally occurring macro molecules
EDX-SEM	Electron dispersal – X ray analysis - Scanning electron microscopy	Electron microscopy combined with elemental and compound analysis using energetic electrons to liberate X rays for analysis.	Identification of materials in surfaces and contaminants present. Particularly useful for metals and ceramics. Verification of deposition of coatings.
GC	Gas chromatography	Separation and identification of	Identification and quantification of organic impurities, monomers,

		volatile compounds.	plasticisers other polymer modifiers etc.
MS	Mass Spectroscopy	Identification of compounds by measuring mass charge ratio of ions.	Identification of chemical structure. Quantification of residual monomers and volatile additives in polymers. Identification of contaminants. Analysis of deposits on explants. Analysis of coatings.
GPC	Gel permeation chromatography	Separation of polymers by transit time through a gel.	Characterisation of raw materials.
HPLC	High performance liquid chromatography	Liquid phase separation by solubility.	Analysis of extractions and leachates: for additives*
ICP	Inductively charge plasma	Detection of elements by excitation in a plasma	Detection of trace metals in extractions particularly for USP testing.
IR	Infra red spectroscopy	Measurement of infra red transmission through a thin film, or reflectance from a surface.	Polymer identification and verification.
NMR	Nuclear magnetic resonance	Detailed analysis of complex molecules by energy measurement of nuclear environment.	Material identification particularly contaminants or controlled release compounds. Polymer and other chemical structure analysis.
UV	Ultra violet spectroscopy	Absorption of UV light	Analysis of extractions and leachates: for additives*. Characterisation of intra ocular lens material.
XPS	X-ray photoelectron spectroscopy	Surface analysis by measuring energy of electrons released by incident radiation.	Examination of surfaces for cleanliness, contaminants and coatings.
XRF	X-ray fluorescence	Similar to XPS but delivered energy results in secondary fluorescence.	Examination of surfaces for cleanliness, contaminants and coatings.

2D PAGE	Gel electrophoresis	Separation of biological compounds by size and polarity in gel media.	Analysis of explants and biofilms.

*Additives that may be found on medical devices or found by extraction include: lubricants, accelerators, monomers, higher molecular weight oligomers (from incomplete polymerisation), residual solvents, degradation products (temperature, absorption, hydrolysis, oxidation, corrosion or dissolution) contaminants (mould release agents, anti-static, anti-stick agents, cleaning chemicals).

Implants

There is a wide array of ASTM[7] standards pertaining to implants; they specify material compositions, corrosion resistance and passivation of metals. There is also FDA Guidance[8] which gives a similar range of testing for re-sorbable implants; this document additionally describes physical testing and life cycle testing.

Tissue Engineered Products

ASTM has produced a number of test method documents for characterising scaffold and functional materials. These include alginates, ceramics, collagen, chitosan, hyaluronan, and a more general test method[9] for the characterisation of scaffolds.

Drug Delivery Devices

Nanoparticles are an area of particular concern in drug delivery. Guidance and standard test methods are yet to crystallise in this area. But, some drug delivery devices have been around for long time: nebulizers, anaesthetic machines, needles etc.. Specific standards are often in force for these items. Also for these devices pharmacopeia monographs and standards, such as USP Chapter 724, can be relevant. There is one for measuring the release of active substances from trans-dermal patches[10].

Less Invasive Devices

Chemical analysis is still important for less invasive devices, especially so if they have coatings or a surface activity (such as antimicrobial). For example PVC tubing has many applications in our market. Often is specified because it softens at body temperature but does not collapse. This property is partly controlled mechanically by tubing diameter and wall thickness, but hoop strength and softening are largely controlled by fillers and plasticisers. These additives need to be accurately defined in development and verified batch to batch in production.

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Summary

Material analysis is essential to the understanding of the performance, lifecycle and structure of any medical device. It is an important aid to development and essential to quality control in production. With tight costing and the increasing competitiveness within the industry, it helps to avoid additional costs, from for example the lost production due to the use of unsuitable materials and the possibility of adverse reactions and/or rejection of the device by the patient. Having a chemical signature for the materials used allows a replacement to be used without the expense of full biocompatibility testing.

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References

[1] B. Sandán, c. Olerud, M. Petrén-Mallmin & S. Lasson, *Hydroxyapatite coating improves fixation of pedical screws,* British Editorial Society of Bone and Joint Surgery, Vol. 84-B, No. 3, April 2002; http://web.jbjs.org.uk/cgi/reprint/84-B/3/387.pdf

[2] Werner A. G., *Short Classification and Description of the Various Rocks (1786)*

[3] Fred H. Albee, *Studies in Bone Growth: Triple Calcium Phosphate as a Stimulus to Osteogenesis.* Ann Surg. 1920 January; 71(1): 32-39

[4] L.L. Hench & J. Wilson, *An Introduction to Bioceramics*, 1993, World Scientific Publishing Co. Pte. Ltd., Singapore

[5] R.J. Furlong & J.F. Osborn, *fixation of hip prostheses by hydroxyapatite ceramic coatings,* J. Bone and Joint Surg., 73-B(3): (1991) 741-745

[6] Polyether ether ketone

[7] ASTM International http://www.astm.org

[8] Guidance document for Testing Biodegradable Polymer Implant Devices, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080265.htm

[9] ASTM F2150-08, *Standard Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products:*

[10] http://www.pharmacopeia.cn/v29240/usp29nf24s0_c724hs30.html

TRANSDERMAL DELIVERY SYSTEMS—GENERAL DRUG RELEASE STANDARDS

Relevant parts of ISO 10993 Biological evaluation of medical devices

- *ISO 10993-14:2001 Biological evaluation of medical devices Part 14: Identification and quantification of degradation products from ceramics*
- *ISO 10993-15:2000 Biological evaluation of medical devices Part 15: Identification and quantification of degradation products from metals and alloys*
- *ISO 10993-16:1997 Biological evaluation of medical devices Part 16: Toxicokinetic study design for degradation products and leachables*
- *ISO 10993-17:2002 Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances*
- *ISO 10993-18:2005 Biological evaluation of medical devices Part 18: Chemical characterization of materials*
- *ISO/TS 10993-19:2006 Biological evaluation of medical devices Part 19: Physico-chemical, morphological and topographical characterization of materials*