INTERFACIAL CHEMISTRY IN WOUND CARE AND BIOSURGERY DEVICES

Aaron D. Strickland, PhD. and Greg Mouchka iFyber LLC, Ithaca, NY

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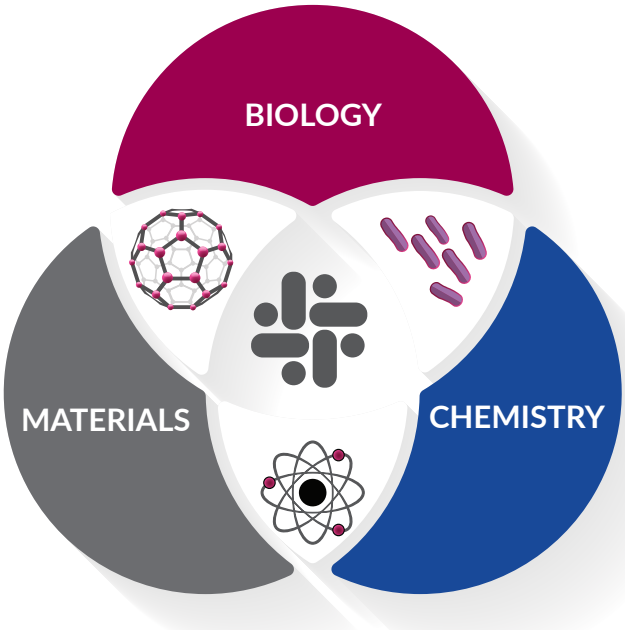
INTRODUCTION

Current medical devices used in advanced wound care and biosurgical applications represent a diverse set of products employing a range of functional materials. Given the complexity of these products, there exists important chemistry that occurs between the various materials making up the device and the environment in which it resides. Collectively, this interfacial chemistry governs design, function, chemical and biological compatibility, process development, and manufacturing. For example, advanced wound care and biosurgical devices can contain unique chemistry at the interface between small molecule actives, biomolecules, functional polymeric materials, metals, and natural matrices. Similarly, there are also interfaces that exist between the device constituents and test methods used to assess device performance, biocompatibility, and overall make up. Not having a full appreciation for these interfaces can lead to costly decisions during the product development process. A few case studies are provided below to illustrate the importance of understanding the interfacial chemistry that occurs at key points in this process.



THE CHALLENGE

CASE STUDY #1:
RESIDUAL TESTING ON A RESORBABLE DEVICE

A resorbable biosurgical material is being developed based on an existing predicate device. The new material behaves significantly differently than its predecessor after gamma irradiation, leading to questions about how the material is affected by sterilization. Testing for residual carbonyl groups (a standard process for irradiated biomaterials) reveals some manufacturing process parameters were potentially not controlled correctly. Going down this decision path means an involved root cause analysis and investigation. *What step in the process was leading to the observed differences between the predicate and new device? How can we identify the offending step and still remain on schedule and within budget?*

CASE STUDY #2:
BIOCOMPATIBILITY TESTING AND FALSE POSITIVES

A wound dressing with active antimicrobial ingredients is being developed to help with a particular skin infection management application. The material shows good in vitro antimicrobial properties, but troubling in vitro cytotoxicity data. Nothing in the literature or similar products on the market would give the developers an indication that the material would be toxic to mammalian cells. *What should we do at this point? Continue on and risk an expensive and time intensive animal study when it may be premature? Take a step backward and re-characterize the method of action of the antimicrobial ingredient?*

THE PROCESS

To help understand how the various interfaces can affect the product, medical device manufactures often enlist the services of contract research organizations (or CROs) to conduct tests for activity, performance, biocompatibility, residual analysis, etc. While these tests are crucial for characterization of the design, many traditional CROs offer only standard test methods, so they are unable to provide the insight that may be warranted for a particular application. Medical device manufacturers would benefit from contractors that offer a 'deeper dive' into a technology, especially when standard protocols and standardized test methods are not appropriate, or do not provide reasonable outcomes. Given the complexity of devices used in advanced wound care and biosurgery applications, knowledge of interfacial chemistry and the ability to creatively apply this discipline to a given technology can be key to successful product development.

iFyber is a contract research firm that has experience working closely with medical device companies by extending their internal development teams to investigate questions and develop answers that are rooted in interfacial chemistry. A myriad of questions should be asked when developing complex medical devices:

- How does a small molecule active interact with the other components of the device?
- What is the fate of an active in the device and as a function of the manufacturing process, sterilization, storage, etc.?
- What is the root cause of device failure and how can this be assessed when the device is comprised of many different material types?
- How can analytical and biological testing be effected by the individual components of the device?
- How is the data supplied from a standard test method affected by attributes of the method itself?

Working with our clients' development teams, iFyber gains contextual understanding of the application, asks questions, performs experiments, analyzes results and provides answers. The case studies above, with iFyber's involvement, had positive outcomes that technical, business, and project teams could appreciate.

THE SOLUTION

CASE STUDY #1:
RESIDUAL TESTING ON A RESORBABLE DEVICE

After a quick study of the methods used to determine carbonyl content, and relating these methods to the interfacial chemistry expected for the device, a reassessment of the carbonyl assay itself was deemed necessary. As it turned out, the standard assay was conducted with the product and assay reagents present at the same time, causing rapid breakdown of the biomaterial and erroneously high values for carbonyl content over a specified timeframe resulting in false positives. Adjusting for this chemistry lead to predictable and acceptable carbonyl content results and gave the device developer the confidence that their manufacturing process was repeatable after all. Development was able to continue without delay.

CASE STUDY #2:
BIOCOMPATIBILITY TESTING AND FALSE POSITIVES

Attention was turned to the standard cytotoxicity test used to evaluate the material; specifically, the MTT assay chemistry used to assess cytotoxicity. Based on solid scientific evidence, an appreciation of the potential compatibility issues between the antimicrobial agent and the MTT assay chemistry used to determine cytotoxicity potential, and some assessments at the bench, an adjustment was made to this assay chemistry, which led to improved in vitro biocompatibility results. Changes were reported to the regulatory agency and development continued to device 510(k) clearance and launch.

INTERFACIAL CHEMISTRY TOOL SET

iFyber has drawn from a number of analytical methods and techniques that can provide significant information regarding the chemistry that is occurring at interfaces relevant to medical devices. The following list provides some examples that are particularly useful in the study of advanced wound care and biosurgical devices.

ANALYTICAL TOOLS

Nuclear Magnetic Resonance (NMR)
data on molecular structure and chemical environment

FT-IR and Raman
molecular structural information; quantitative and quantitative assessment of analytes

Electron Paramagnetic Resonance (EPR)
information on free radicals and the surrounding environment

UV/Vis
used for colorimetric assays, turbidity measurements, kinetic assays, particle sizing, and bacterial assays

Dynamic Light Scattering (DLS)
data on particle size in solution and surface charge

IMAGING TOOLS

Transmission and Scanning Electron Microscopy (TEM/SEM)
images material, and elemental makeup when coupled with spectroscopic techniques

Fluorescence Imaging (standard and confocal)
assessing cellular function in response to an active agent

RHEOLOGIC TOOLS

BET Surface Area and Porosimetry
data on the surface area and porosity of materials

Thermogravimetry (TGA) and differential scanning calorimetry (DSC)
insight into heat transfer and material stability

ASSESSMENT OF AN IMPLANTABLE DEVICE USING NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

iFyber has developed a new method for assessing the extent of light activated polymerization for a resorbable photopolymer coating used in adhesion prevention applications. Using Nuclear Magnetic Resonance (NMR) Spectroscopy and novel sampling, iFyber scientists helped guide the manufacture of an implantable medical device. NMR is sensitive to the number of nuclei within a given molecule (i.e., 1H and 13C atoms) The signals from these nuclei occur at unique regions of the NMR spectrum (referred to as chemical shift) based on the surrounding chemical environment (i.e., neighboring atoms). In this application, NMR analysis provided qualitative and quantitative information on the extent of reaction for a well-known light induced polymerization reaction of vinyl acetate. By monitoring the intensity of the signals produced from the vinyl groups in the photopolymer coating, a number of parameters were optimized, including the polymer formulation (e.g., catalyst, monomer concentrations), polymerization time, and the light intensity needed to polymerize the coating without compromising the performance of the implantable device. Ultimately, NMR was used to guide manufacturing specifications and the method was validated for Operational Qualification (OQ) and Performance Qualification (PQ).

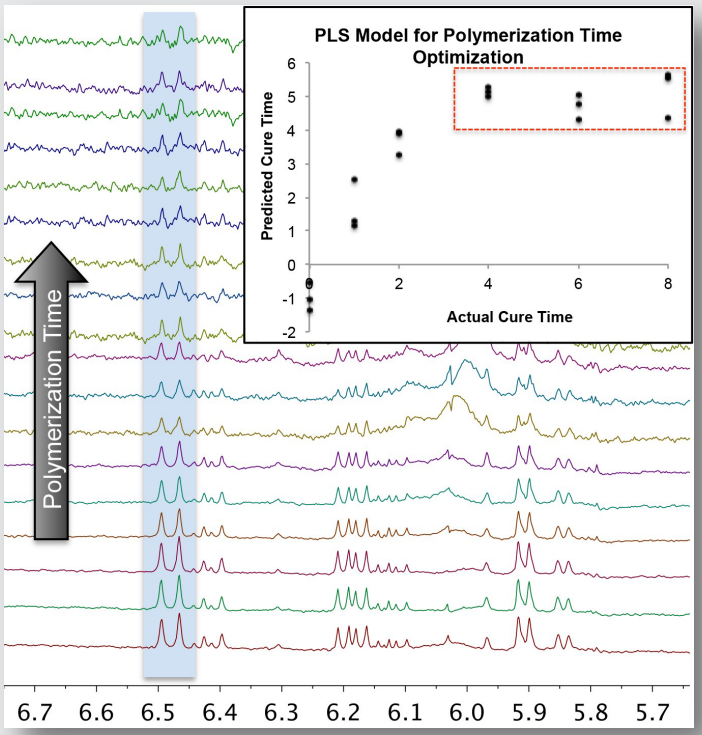


Figure 1. Representative NMR spectra of photopolymer coatings as a function of cure time. The region highlighted in the blue box represents diagnostic signal for the vinyl groups of the photopolymer system that were monitored to track various aspects of the coating process. The inset shows results from partial least squares statistical model used to determine the minimum time needed to maximize photopolymerization (red dotted box)