Failure analysis in medical applications of polymeric materials

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• Cambridge Polymer Group, Inc. is a contract research laboratory specializing in materials and products. Our services range from routine analytical testing to new product research and development.

• Failure analysis of plastics and medical devices
Case Study 1: Contact Lens Solution

• Around 2005-2006, CDC began observing a number of patients contracting fusarium keratitis
  – Infection of the cornea from a fungus
  – 130 confirmed cases

Multistate Outbreak of *Fusarium* Keratitis Associated With Use of a Contact Lens Solution

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• 68% of patients were using a B&L combination lens cleaner/disinfectant
  – Renu with MoistureLoc
**Multi-Purpose Lens Solutions**

- Alexidine dihydrochloride (preservative/antimicrobial)
  - 4-5 ppm
- Pluronic F127, Tetronic 1107 (surfactant/cleaner)
  - 3%
- Polyquarternium-10 (quaternized hydroxyethyl cellulose/comfort)
  - 0.02%
- HDPE bottle
  - Gamma sterilized
  - Irganox 1076 stabilized

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Theories on what caused the fusarium outbreak

- Anionic radiation products were generated in the HDPE bottle due to the incorrect antioxidant.
- Pluronic solubilized these anionic products in micelles.
- The cationic Alexidine was then sequestered by these anionic products, reducing the antimicrobial efficiency of the solution.
**Additional Theories**

- Processing aids (stearic acid, sodium lauryl sulfate) can desorb into the solution, and deactivate the Alexidine.
- Metal ions are released during the radiation process that interact with the ingredients of the solution.
- The HDPE is oxidizing, along with the plasticizers in the HDPE.
- The pluronic is oxidizing.
- The pluronic is adhering to the walls of the HDPE bottle in the form of gels.
Analysis to support these theories

- Time of flight-secondary ion mass spectroscopy (TOF-SIMS) on bottle (potential stearic acid-type structure)
  - Non-quantitative
  - Not performed on the solution itself
  - ID confidence level never indicated (could be less than 5%)

- FTIR showed carbonyl formation on the HDPE surface
  - No idea how long the polymer chains are containing the HDPE
  - Not performed on the solution

stearic acid: m/z = 283
Problems with the Alexidine Inactivation Theory

- All batches of MoistureLoc would be affected and would have reduced biocidal efficacy
  - All field returns that were tested met the required biocidal efficacy for *fusarium solani*.

- One facility was sterilizing the bottles with ethylene oxide.
- Testing was also performed in PET bottles. No difference in fusarium killing efficacy.
- B&L performed extractions of the HDPE, then reconstituted with MoistureLoc and assayed with *fusarium solani*. All were still effective.
Other Theories

- Processing aids (stearic acid, sodium lauryl sulfate) can desorb into the solution, and deactivate the Alexidine
- The HDPE is oxidizing, along with the plasticizers in the HDPE.
- The pluronic is oxidizing
- The pluronic is adhering to the walls of the HDPE bottle in the form of gels.
- Metal ions are released during the radiation process that interact with the ingredients of the solution

Testing showed these compounds cannot deactivate Alexidine

Most solutions use HDPE bottles; no plasticizers

All contact lens solutions contain pluronics in a similar concentration

What??
So What Did Happen?

• B&L performed extensive non-compliance testing
  – Topping off lens cases (e.g. after removal of lens, just adding more solution).
  – Reuse of solution
  – Allowing solution to dry in case
  – Improper cleaning of lens cases
  – Inadvertent introduction of soap into solution
• Inoculated cases with *fusarium solani*

• Inadequate fusarium disinfection occurred when:
  – Multiple re-uses of the same solution in the lens case
    • Depletes Alexidine
  – Allowing a full lens case to dry, then re-using
    • Film prevents biocidal efficacy of Alexidine
**Summary**

- Occam’s razor: the simplest theory is usually the right one.
- The Plaintiff’s theories were never born out in terms of biocidal inactivation, and were complicated.
- Patient non-compliance did result in biocidal inactivation.
  - Survey* performed indicated that the majority of patients are non-compliant with the IFU (99.6%).

*Robertson, Cavanaugh, “Non-compliance with contact lens wear and care practices: a comparative analysis”, Optom Vis Sci, 2011*
Case Study 2: Syringe cracking

- Polycarbonate syringes were showing haziness and microcracks near luer tip following accelerated aging at 55°C

- Features
  - UV-curable adhesive in luer
  - ABS plunger
  - Aging in humid environment
  - ETO sterilized
  - Manufactured ex-US
  - Never seen in non-aged samples

- Theory
  - Environmental stress cracking due to unreacted monomer or leachable from ABS plunger
What did we try

- New vs. aged samples that showed haziness/cracking
- FTIR
- SEM (Image)
- Replicate the process
- DOE
- Influence of plunger
- Investigated manufacturing process details
  - Gloves vs. no gloves
  - IPA wipe
  - UV cure time
SEM Images

10935-1
EXTERIOR

10935-2
EXTERIOR

clear

hazy
FTIR

surface residue from 10935-2 scraped from hazy region

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DSC on ABS

Newly prepared

Aged 13 weeks
DSC on epoxy

Newly prepared

Aged 13 weeks
TGA on components of syringe

Modest increase in mass loss in freshly cured epoxy
Clue into manufacturing deviations
Manufacturing review

- Some shifts were not wearing gloves during assembly
- Some shifts were wiping the PC barrels with IPA after assembly
- Some variability in UV cure time
**Test Study**

- **Variables**
  - Model hand oil (palmitic acid, stearic acid, oleic acid, cholesterol)
  - IPA
  - Unreacted epoxy monomer
  - ABS plunger present
  - Relative humidity (low, high)
  - Sterilization
- **Aged at 55°C for up to 5 weeks, taking out and examining for haziness and cracks every week**
Conclusions of Study

- IPA wiped samples showed no hazing or cracking
- Plunger presence did not affect the appearance of hazing or cracking
- Unreacted epoxy monomer caused hazing and microcrack formation
- ETO Sterilization appeared to create a greater likelihood of cracking formation
- Humidity only affected cracking when sterilization occurred
- Hand oil caused haziness at high humidity, sterilized

No single variable was responsible for the failures; a combination of conditions.
**Client Outcome**

- Changed manufacturing procedure
  - All manufacturers wear gloves, use IPA wipe
- Tightened curing time procedure for epoxy
**Case Study 3: We have contamination and/or oxidation!**

- Manufacturing residue left on components
- Oxidation of implants
Metallic Device Analysis

InterOp™ Acetabular Shell

Extract with solvent

FTIR

GC-MS

fatty acids

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Synovial fluid contains palmitic acid and oleic acid

Fatty acids in synovial fluid (SF) and inflammatory markers in SF and serum from patients with inflammatory joint diseases

- With focus on correlation of n-6 and n-3 polyunsaturated fatty acids to SF cytokines interleukin (IL)-6 and IL-12 and serum C-reactive protein

BY
RUBINA OLESEN
MASTER THESIS IN HUMAN NUTRITION
2008

Fatty acid fractions in synovial fluid in rheumatoid and osteoarthritic patients

Sugiyama, Ono, “Fatty Acid Metabolism in the synovial fluid in the patients with rheumatoid arthritis and osteoarthritis”, (1966).
Device Absorption of Biological Fluids

- Apolar species in synovial fluid readily absorb into UHMWPE and metal implants
- Cholesterol, squalene, fatty acids

UHMWPE Explant analysis

UHMWPE Tibial Insert

Heavily oxidized due to gamma sterilization
Oxidation levels in explants

- Absorbed lipids and fatty acids can look like oxidation
- Remove with soaking in hexane, heptane.

Currier et al, JBJS, 92A, 2411 (2010)
Outcome

- Assess what SHOULD be on an explanted medical device, vs. what shouldn’t be
  - E.g. biological fluids vs. manufacturing compounds
- Remove the biological fluids, and see what is left
Case Study 4: Creep vs. Wear in Hip and Knee Implants

- Highly crosslinked UHMWPE introduced in the late nineties
  - Greatly improved wear resistance of these implants
- How has this affected analysis of retrievals?
Wear Analysis of UHMWPE

Scratching
Pitting
Delamination
Abrasion
Polishing
Loss of Machine Marks
Implant retrievals of highly crosslinked devices

New

Post-Melting

After Retrieval

Is this wear?
Melting of UHMWPE

Room Temperature

160°C

Room Temperature
Global Shape Memory

UHMWPE Pins

Plastic Deformation

After Melting
Metal letter-die  | Razor blade  | Blunt tool  | Microtome
Longevity explant (54 months in vivo)

- Removed because of dislocation
- No oxidation
- No changes in crystallinity
For More Information

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Some images courtesy of Massachusetts General Hospital