Considerations for Ophthalmic Drug Products in Semi-Permeable Packaging

Christopher T Houston
Bausch + Lomb

Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products (PODP)
February 22-23, 2011

Overview

- Ophthalmic packaging systems
  - Dosage forms
  - Primary versus secondary packaging
- Case studies and examples
  - Summary of PODP extraction of LDPE
  - Types of leachables commonly observed
  - Typical leachable sources
  - Lessons learned
- Conclusion

Ophthalmic Packaging

- Ophthalmic drug product dosage forms:
  - Ophthalmic solutions and suspensions (focus for today)
  - Ointments
  - Implantable devices
  - Intravitreal injection
- Primary packaging for most solution and suspension dosage forms are similar:
  - Bottle (pre-formed or blow-fill-seal) is typically LDPE
  - Tips and caps are often harder plastic materials such as LLDPE, HDPE, or PP



PODP Extraction Study of LDPE

- LDPE extracted in PODP protocol
  - Most relevant material in protocol for topical ophthalmic solution and suspension primary packaging
  - Known additives:
    - Irganox 1010, Irgafos 168, BHT, Ca stearate, erucamide, Chimassorb 944
- Extraction paradigms
  - Water (pH 2.5, pH 9.5), 50/50 isopropanol / water, isopropanol, and n-hexane
  - Sonication, headspace, sealed vessel, reflux, and Soxhlet
  - Headspace GC, GC-FID and -MS, HPLC-UV and MS, ICP-MS

Christopher T Houston
PQRI E & L
Bethesda 23/02/2011

PODP Extraction of LDPE

Selected Extractables	Hexane Reflux & Soxhlet	Isopropanol Reflux & Soxhlet	Isopropanol / Water Sealed Vessel	Aqueous (pH 2.5, 9.5) Sonication
Irganox 1010	X	X	X	
Irgafos 168	X	X	X	
Irgafos 168, oxidized	X	X	X	
BHT	X	X	X	
Stearic acid	X	X	X	
Erucamide	X	X	X	X
DEHP	X	X	X	
Stearamide	X	X		
Palmitic acid	X	X	X	

Green = anticipated additives, X = observed in extracts

Christopher T Houston

PQRI E & L
Bethesda 23/02/2011

PODP LDPE Extraction Summary

- All anticipated additives detected, along with evidence for Chimassorb breakdown products
  - Also observed additive transformation products (e.g., oxidized Irgafos 168)
  - Observed related substances to known additives (e.g., palmitic acid)
- Unanticipated extractables detected (e.g., DEHP)
- Less vigorous extraction (water / sonication) did not reveal any significant extractables except erucamide
  - Best practice recommendation: for ophthalmic packaging, water should not be the sole extraction solvent
  - Use of water only does not…
    - …account for solubility modifiers in the formulation
    - …impart strong understanding of the material

Ophthalmic Primary Packaging

In practice…

- Properties of LDPE as a primary package:
  - LDPE used in ophthalmics usually contains minimal additives
    - Few, if any, significant extractables when examined by multiple solvents and analytical techniques
    - Plastic degradation products in the form of aliphatic acids somtimes observed in unstabilized LDPE resin
- HDPE or PP (i.e., screw cap) properties
  - Common extractables include antioxidants, slip or anti-stat agents, colorants, optical clarifiers
    - Consistent with LDPE extracted in PODP protocol
  - Caps have minimal contact with formulation
- Extractables from primary packaging seldom observed as drug product leachables at *significant levels*

What are “Significant Levels”?

- The FDA reporting threshold for individual leachables is 1 ppm (µg/mL)
- What do the levels look like if a 0.15 µg/day SCT is applied consistent with PQRI OINDP recommendations?

Doses/day	Est. AET Leachable (µg/container)	Est. AET Leachable (µg/mL)	Est. AET Extractable (µg/g bottle)
2	13.9	2.8	5.3
4	6.9	1.4	2.7
6	4.6	0.93	1.8

Assumptions: 5 mL product in a 7.5 mL, 2.6 g LDPE bottle, dose = 27 µL (185 doses / bottle)

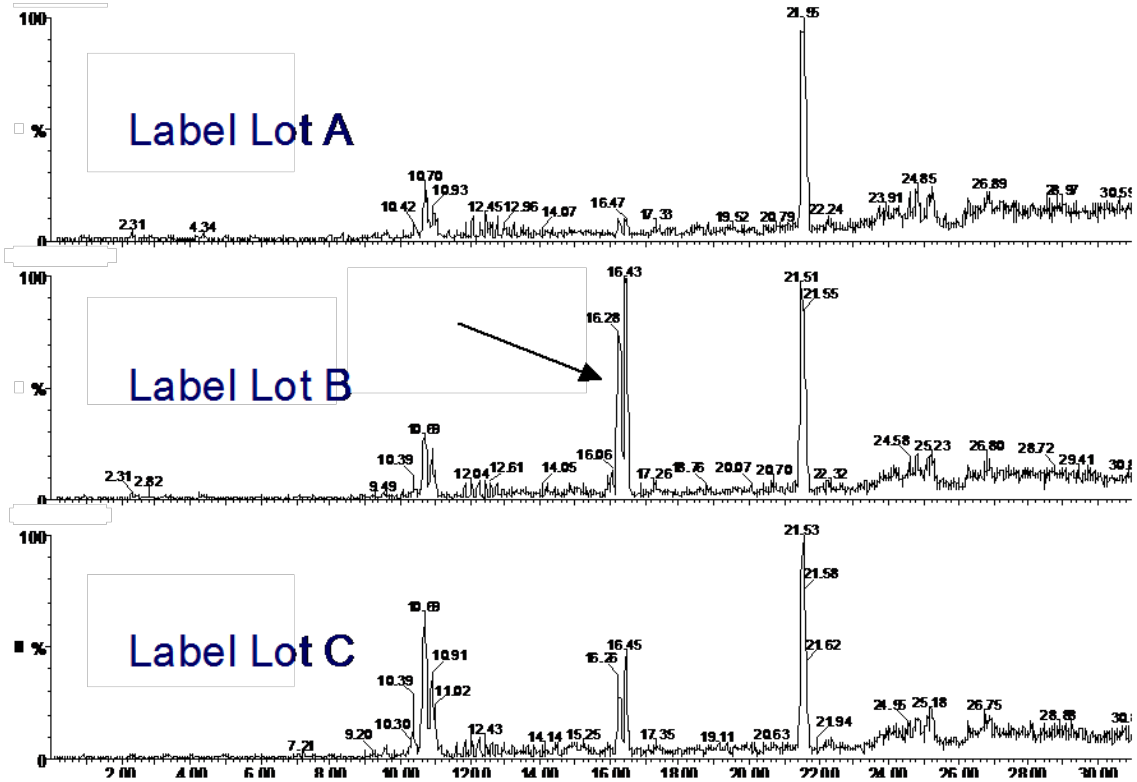
Semi-Permeable Packaging

- Although PQRI-OINDP thresholds have not historically been used in Ophthalmology for FDA, AET levels for leachables are within the same order of magnitude as FDA 1 ppm reporting guideline
- In practice, primary ophthalmic packaging shows few – if any – significant extractables
- However, LDPE is semi-permeable
- Experience demonstrates that secondary packaging has the most significant impact on drug product leachable profiles in semi-permeable systems

- The following case studies are examples of leachables observed in developmental formulations over the past eight years

Case Study #1: Acrylate Ester

- Scenario:
  - Labels with UV-cured ink contain a pair of acrylate esters that can leach into product
  - Levels vary across label lots



Extracted ion chromatograms (m/z 265) of label extracts

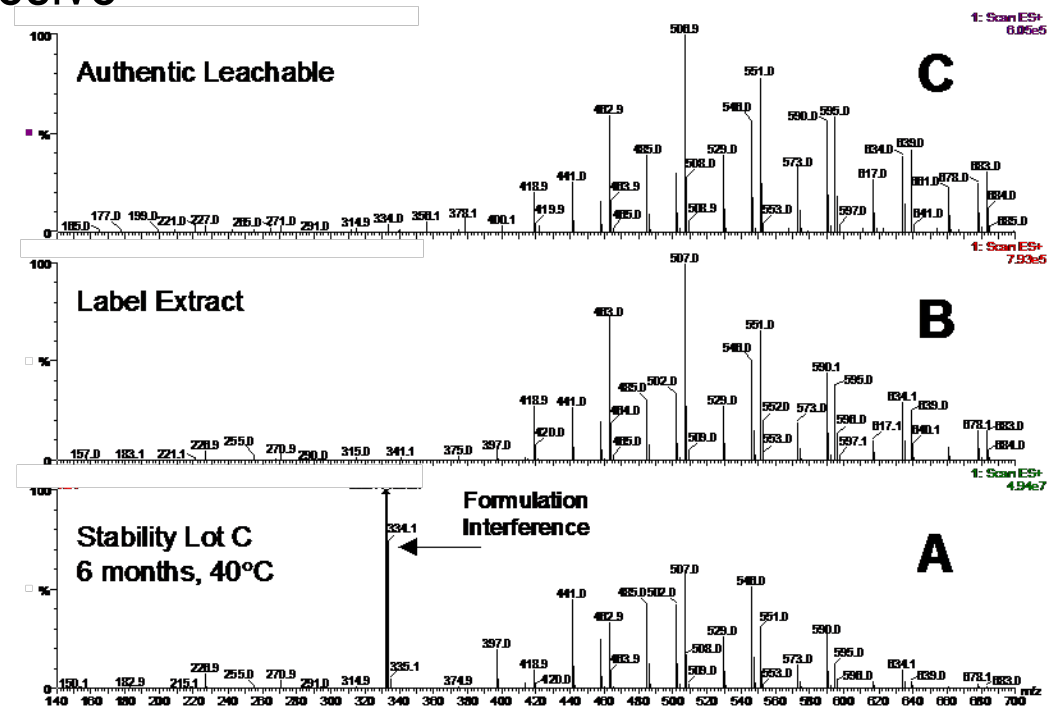
Christopher T Houston
PQRI E & L
Bethesda 23/02/2011

Case Study #1: Acrylate Ester

- Observations:
  - Compounds used to adjust ink viscosity for printing; amount varies with ink lot
  - Levels peaked at 0.4 ppm in product and decreased steadily over time, dropping below 0.2 ppm within 6 months
- Lessons Learned:
  - Analysis of three batches of packaging materials can capture vendor variability that might otherwise go unnoticed
    - Implications for batch-based limits (FDA)
  - Leachables from secondary packaging materials do not always trend upward

Case Study #2: PEG-Related

- Scenario:
  - A polyethylene glycol derivative migrated into drug product after six months of stability
  - Leachable identified as a proprietary surfactant in label adhesive

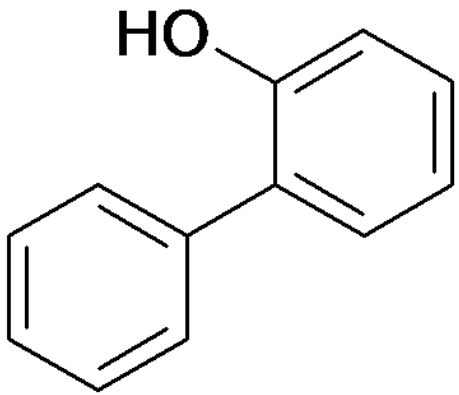


Case Study #2: PEG-Related

- Observations:
  - Material not a small molecule, MW ranged from ~400 - 600
  - Leachable level increases slowly over time
  - At 18 months, the leachable reached 1 ppm
- Lessons Learned:
  - A common perception is that secondary packaging leachables are always small, volatile substances
  - Lower volatility compounds in intimate contact with semi-permeable containers can migrate into product
  - Leaching behavior very different from acrylate
    - Acrylate: Rapid increase, followed by decrease
    - PEG-Related: Slow increase over time

Case Study #3: o-Phenylphenol

- Scenario:
  - Leachable appeared after nine months of room temperature stability
    - On accelerated stability, did not appear at all
  - Identified as o-phenylphenol (OPP) from SBS board used to make unit cartons
  - OPP is formulated into SBS board as a fungicide / sterilization agent to facilitate paper storage



Christopher T Houston
PQRI E & L
Bethesda 23/02/2011

Case Study #3: o-Phenylphenol

- Observations:
  - Leachable source particularly difficult to identify because of analyte vapor pressure
    - Extraction studies of cartons and individual raw materials were free of OPP
  - Key observation:
    - Unit cartons from the stability chamber test positive for OPP
    - Unit cartons removed from chamber and allowed to sit on lab bench for a few weeks test negative for OPP
    - Outgassing
  - Sampling and shipping measures taken to minimize sample outgassing required to solve problem

Case Study #3: o-Phenylphenol

- Lessons Learned:
  - Product in semi-permeable primary packages can be impacted by secondary packaging in close proximity
  - Approach accelerated E&L studies with caution
    - For OPP, higher temperature studies actually minimized the appearance of leachable
  - Sampling / shipping methods must be carefully designed to ensure reliable extractable testing of secondary packaging materials

Case Study #4: Diethyl Phthalate

- Scenario:
  - Diethyl phthalate (DEP) leached into a formulation after 12 months of stability
  - Not previously observed as an extractable
  - The source of the diethyl phthalate was determined to be a carton tab seal (tape) added as unit carton tamper evidence
- Observations:
  - Tape film vendor initially claimed “no phthalates”, then admitted the film formulation contained 18% DEP

Case Study #4: Diethyl Phthalate

- Lessons Learned:
  - Components that do not make intimate contact with the primary package can nevertheless impact leachable profiles
  - Tab seal was installed for a niche market at the request of a particular government
    - Bypassed R&D
    - DEP never flagged as a potential extractable
  - Follow-up work leveraged headspace GC as a screening method to identify new candidate material

Recommendations

- Thorough understanding of packaging extraction profiles requires multiple solvents
  - Significant prior art relying on water alone
  - Implications for EP compliance – understanding additives, etc
- For ophthalmic drug products in semi-permeable containers, secondary packaging becomes a critical item for E&L
  - Components must be handled appropriately for reliable extraction results (OPP outgassing example)
  - Variability often exists (acrylate example)
  - Leaching behavior is highly diverse
    - No single model for accelerated studies (acrylate vs PEG)
    - Acceleration can actually minimize appearance of volatile leachables (OPP example)
  - Proactive component screening is critical (DEP example)
    - Quality by Design
- Discussion point – what are the relative merits of 1 ppm vs the PQRI-OINDP threshold approaches?