The journey of a polymer producer to support customers E&L needs

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COMPLIANCE IS NOT ENOUGH: THE JOURNEY OF A POLYMER PRODUCER TO SUPPORT CUSTOMERS E&L NEEDS

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• Introduction: SABIC and the Healthcare Industry

• Extractables: Setting up of the procedures
  • Analytical techniques and LOD
  • Influence of extracting solvent (polarity, pH)
  • NIAS, additives ("stabilizers")

• Sterilization Study
  • Introduction on main sterilization techniques
  • Focus on gamma-radiation sterilization
  • Influence of radiation on LDPE and HDPE
INTRODUCTION – SABIC AND THE HEALTHCARE INDUSTRY
SABIC IN NUMBERS

1976, our beginning
40 years of growth

4th largest global diversified chemical company*
113th largest public company in the world*

87.53 B$ total assets
39.49 B$ annual revenue
5 B$ net income

40,000 employees
50 countries
5 Strategic Business Units

64 world-class plants worldwide
5 key geographies with innovation hubs
150 new products each year
10,960 global patent filings

*A high rate of growth: reaching 70.4 M metric tons in 2015

Innovative Plastics: 1.505
Performance Chemicals: 0.476
Metals: 5.869
Fertilizers: 6.848
Polymers: 11.673
Chemicals: 43.354
GLOBAL POLYOLEFIN MARKET

Global Healthcare Polyolefin Demand, KT

- Healthcare: 98.33% (150,444) * 2556
- HC Medical (EP/USP compliant): 0.72% (1,097) ***
- HC Non-Medical (Non-Medical grade): 0.95% (1,459) ***
- Global Non-HC PO: 0.95% (1,459) ***
- Global HC Non-medical: 0.95% (1,459) ***
- Global HC Medical: 0.72% (1,097) ***

* Source: BCC Research 2013  ** SABIC’s market research  *** SABIC estimated

Building bridges – understanding each others’ languages
SABIC’S BROAD MATERIALS PORTFOLIO FOR THE HEALTHCARE INDUSTRY

### Manufactured by SABIC

#### High Performance
- **ULTEM™ HU (PEI) resin**
  - Heat resistance
  - Excellent mechanical properties
  - Excellent chemical resistance

#### Engineering Thermoplastics
- **LEXAN™ HP (PC) resin**
  - Excellent processability
  - Transparency
  - Excellent impact resistance

#### Commodity
- **CYCLOY™ HC (PC/ABS) resin**
  - Excellent processability
  - Colorability and aesthetics
  - Good impact resistance

- **CYCOLAC™ HMG (ABS) resin**
  - Cost effective offering good mechanical properties

- **NORYL™ HN (m-PPE) resin**
  - Good impact resistance
  - Hydrolytic stability
  - Broad chemical resistance

#### Thermoplastic Copolymers
- **PC COPOLYMERS**
  - PC
  - m-PPE
  - PC/ABS
  - PC/ASA

#### Thermoplastic Blends
- **LCP**
  - LCP
  - LCP/PS

#### Thermoplastic Homopolymers
- **PEI**
  - PES
  - PPSU

#### Crystalline Thermoplastics
- **PEEK**
  - PPA
  - PBT
  - POM
  - PA

#### Amorphous Thermoplastics
- **PPS**
  - PS
  - PC/PBT
  - PC/PET

#### Specialty Compounds
- **LNP™ specialty compounds**
  - Inherent lubricity, strength, stiffness or conductivity in a wide range of polymers

- **XENOY™ HX (PC/PBT) resin**
  - Good processability
  - Excellent chemical resistance

- **VALOX™ HX (PBT) resin**
  - Good dielectric strength
  - Excellent chemical resistance

- **XYLEX™ HX (PC/PET) resin**
  - Good processability
  - Good chemical resistance
  - Transparency

- **SABIC® PCG (PP and PE) grades**
  - Cost effectiveness
  - Versatility
  - Processability
COMPLIANCE IS NOT ENOUGH: THE JOURNEY OF A POLYMER PRODUCER TO SUPPORT CUSTOMERS E&L NEEDS

EXTRACTABLES: SETTING UP THE PROCEDURES
E&L : OUR UNDERSTANDING

- The terms **extractable** and **leachable** provide clarity in terms of:

  1. The potential versus the actual impact of the product on its user.
     - **Extractable** = possible impact; **Leachable** = actual impact

  2. The object on which the testing is performed.
     - **Extractable** = test the material; **Leachable** = test the final product

- Healthcare market: large diversity of active ingredients, ways of administration (inhalation, injection, ophthalmic, nasal, oral,…)

- No specific standards defined by authorities (US/FDA, EU/EP)

- Pharmaceutical toxicologists use guidelines to predict the leachables that come close to the threshold levels in the different applications

Product Quality Research Institute (PQRI) is the benchmark for the pharmaceutical industry defining the guidelines for extractables and leachables studies. These studies are the basics for the toxicologists.
EXTRACTABLES: 1st STEP TO OUR JOURNEY

Customers’ parameters/requirements
- Multitude of drug/medicine type
e.g. various polarities, chemical stability
- Different drug formulation
Most organic compounds not well soluble in water → different medium
- Which application intended
e.g. Ophthalmics, injectables, inhalation
- Safety Concern vs Analytical Evaluation Thresholds to establish
- Which sterilization technique
Mechanical, chemical, radiation

SABIC internal questions
- Which extracting solvents?:
For extractable to cover leachable
- Does pH have an influence?:
Water at 3 different pH studied
- Which analytical techniques?
To cover maximum extractables
- Which LOD?
Is lower always better?
- Influence of gamma-ray sterilization
Study on LDPE, HDPE

1st step of our journey to answer such questions

• Large span of customers with their own requirements
• Guidelines but no strict extractables regulations
EXTRACTABLES: HOW TO COVER THEM ALL?

**CHALLENGE:**
Find test conditions and analytical techniques to fulfill complex needs

Large span of MW and volatilities to cover

Analytical techniques to cover apolar and polar compounds

Extracting solvents to cover broad range of polarities

- **VOC**
- **SVOC**
- **NVOC**

Potential chemicals of concern

Molecular weight range of extractables

MW: 100 ~200 ~600 1500 Da

BP: 50 ~250 ~500 °C

Potential chemicals of concern

- Aliphatics HC
- **overlap**
- Fatty acids-ester/amide
- Phenolics
- Acids/amines
- Ionic species

**MW:**
- Low MW: ~150
- Intermediate MW: ~250
- High MW: >~250

**BP:**
- Low MW: ~50 °C
- Intermediate MW: ~250 °C
- High MW: >~500 °C

Extracting solvents to cover broad range of polarities

- n-Hexane
- DCM
- iPrOH
- EtOH
- WATER

*Polarity scale based on $E_T$: C. Reichardt, Chem. Rev. 1994, 94, 2319*
LIST OF EXPERIMENTS

**Background:** SABIC has conducted various “Extractable profile studies” on LDPE, HDPE and PP (healthcare grades) using different solvents and different analytical techniques to cover broad range of volatilities and polarities.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>BP</th>
<th>GC-MS</th>
<th>UPLC-HRMS (+ &amp; - APCI)</th>
<th>Headspace GC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>78 °C</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>DCM</td>
<td>40 °C</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hexane</td>
<td>69 °C</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Water pH 2, 7, 9</td>
<td>100 °C</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Neat</td>
<td>115 °C</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

- Extraction performed on polymer granules at reflux
- Combination of HS-GC-MS, GC-MS and UPLC-HRMS to cover most organic extracts
LDPE IS “ADDITIVE FREE” BUT CONTAINS NIAS

Typical LDPE producer needs:

**Peroxides:** Chemicals to be brought in the system with a solvent
- No traces of peroxides found in Extractables but solvent can be seen
- Solvent usually organic species which can be seen in the extractables

**Lubricant:** Hypercompressor needed to reach 2000 bars: use of lubricant
- Traces of lubricant (usually few ppm in nVOC) can end up in the polymer

**Chain Transfer Agent:** Helps to control MW of the polymers
- Can be incorporated in the polymer/oligomer and be extracted at ppm levels in VOC

Example of use of propion-aldehyde as a CTA:
Pattern of 3-ketones with increment of 2C

\[ R = C_{2n} \text{ alkyl chain} \]
with \( n = 6 \) to 16
Some grades use stabilizing additives for processing and sterilization.

Degradation products can be generated (NIAS).

“Primary” and “Secondary” antioxidant commonly used (e.g. Irganox 1010 and Irgafos 168)


M. A. Ruberto; BioProcess International, Chapter 3 Materials and methods; April 2010, pp 36-41
EXTRACTABLES IN “APOLAR” SOLVENTS

sVOC Extractables in Hexane almost exclusively “aliphatic hydrocarbons”
• Hexane powerful solvent to extract material’s oligomers
• Lower LOD would not give extra information and will bring only unnecessary complexity (increasing analytical efforts, thus time and price of the study)

Amount of Extractables is material dependent:
• “easier migration” of low MW compounds in amorphous polymers

Extracts of HDPE in DCM (LOD 1 ppm)  Extracts of LDPE in DCM (LOD 1 ppm)

Extracts of HDPE in Hexane (LOD 1 ppm)  Extracts of LDPE in Hexane (LOD 1 ppm)
EXTRACTABLES IN POLAR SOLVENTS

Extractables in UPW:
- Little to no species detected if additive free. Polymer additives (polar) can be extracted.
- LOD down to 0.05 ppm can be achieved

Influence of pH on fatty acids extraction (SVOC and NVOC)

<table>
<thead>
<tr>
<th></th>
<th>SVOC</th>
<th>NVOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPW</td>
<td>sum fatty acids (ppm)</td>
<td>sum fatty acids (ppm)</td>
</tr>
<tr>
<td>pH 2</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>pH 7</td>
<td>0.4</td>
<td>5.7</td>
</tr>
<tr>
<td>pH 9</td>
<td>0.8</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Does pH have an influence?: Yes as pH = pKa + log [B]/[A]
- Solubility of some organic compounds pH dependant:
- Fatty acids (pKa~9), phenols (pKa~10) are better extracted at high pH (≥7)
- Amines (4 < pKa < 11) are better extracted at low pH
But…

Overall, UPW at pH 7 with a LOD of 0.05 ppm is sufficient for detection purposes
COMPLIANCE IS NOT ENOUGH: THE JOURNEY OF A POLYMER PRODUCER TO SUPPORT CUSTOMERS E&L NEEDS.

STERILIZATION STUDY
STERILIZATION TECHNIQUES - 4 BASIC APPROACHES

Gamma / E-Beam Radiation
- Irradiation by either a Cobalt source gamma rays or an electron beam (E-Beam)
- Absorption of energy (dose delivery) destroys the microorganisms

Ethylene Oxide EtO
- Used to sterilize temperature and moisture sensitive medical devices
- EtO residue must be removed after sterilization
- Lengthy cycle / aeration time

Autoclave 121-134°C
- Microorganisms killed with saturated steam under pressure
- Cannot be used for moisture sensitive devices

Hydrogen Peroxide Gas (ASP STERRAD† & Steris V-Pro †)
- Low temperature, hydrogen peroxide gas
- Used for heat and moisture sensitive items
- Fast cycle times compared to EtO
RELATIVE STABILITY OF MEDICAL POLYMER FAMILIES POST RADIATION STERILIZATION


Polyolefin oxidation caused by \( \gamma \)-sterilization

\[
\begin{align*}
P & \xrightarrow{\text{gamma rays}} P \cdot \\
P \cdot & \xrightarrow{O_2} PO_2 \cdot \\
2 PO_2 \cdot & \rightarrow POOP + O_2 \\
PO_2 \cdot & \rightarrow POOH + P' \cdot \\
POOP' & \xrightarrow{\text{gamma rays}} P-CHO + P'O \cdot
\end{align*}
\]
STERILIZATION STUDY: LDPE VS HDPE (HEALTHCARE GRADE)

- HDPE: Injection molding, caps and closures and other parts for medical packaging
- LDPE: Injection molding, caps and closures (additive free)

<table>
<thead>
<tr>
<th>Headspace GC-MS (VOC)*</th>
<th>GC-MS (SVOC)*</th>
<th>LC-MS (NVOC)*</th>
<th>Weight loss</th>
<th>GPC analysis</th>
<th>FT-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>DCM</td>
<td>DCM</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Extractables LDPE (additive free)

<table>
<thead>
<tr>
<th></th>
<th>before Irradiation (mg/kg)*</th>
<th>After Irradiation (mg/kg)*</th>
<th>After – before (mg/kg)</th>
<th>% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOC (sum aliphatic HC)</td>
<td>9,3</td>
<td>8,3</td>
<td>-1</td>
<td>-11%</td>
</tr>
<tr>
<td>sVOC (Sum aliphatic HC)</td>
<td>747</td>
<td>608</td>
<td>-139</td>
<td>-19%</td>
</tr>
<tr>
<td>nVOC ((+) &amp; (-))</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

LDPE: Slight reduction of VOC and sVOC after irradiation (all are aliphatic HC)

Extractables HDPE (use of additives)

<table>
<thead>
<tr>
<th></th>
<th>before Irradiation (mg/kg)*</th>
<th>After Irradiation (mg/kg)*</th>
<th>After – before (mg/kg)</th>
<th>% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOC</td>
<td>5</td>
<td>20</td>
<td>15</td>
<td>300%</td>
</tr>
<tr>
<td>Sum sVOC</td>
<td>162</td>
<td>181</td>
<td>19</td>
<td>12%</td>
</tr>
<tr>
<td>Sum nVOC (+)</td>
<td>57</td>
<td>33</td>
<td>-24</td>
<td>-42%</td>
</tr>
<tr>
<td>Sum nVOC (-)</td>
<td>79</td>
<td>24</td>
<td>-55</td>
<td>-70%</td>
</tr>
</tbody>
</table>

HDPE additives are mostly responsible of increase of VOC and sVOC while nVOC are decreased

* Limit of Detection: 1 mg/kg
WEIGHT LOSS AND MWD

Weight loss

<table>
<thead>
<tr>
<th></th>
<th>LDPE (mg/kg)</th>
<th>HDPE (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before irradiation</td>
<td>7000</td>
<td>1000</td>
</tr>
<tr>
<td>After irradiation</td>
<td>6000</td>
<td>1000</td>
</tr>
<tr>
<td>Weight loss difference</td>
<td>1000</td>
<td>0</td>
</tr>
</tbody>
</table>

- Weight loss measurements confirmed that nothing is lost in HDPE, just transformed
- LDPE mass loss probably due to release of volatiles due to irradiation

GPC

- Little impact of irradiation on molecular peak (Mp) and and average molecular weight (Mn) for both grades
- High impact on polydispersity for LDPE (little impact of HDPE)
- Additives in HDPE efficiently protects polymers from degradation
GAMMA RAY EFFECT ON BRANCHING BY HT-GPC/VISCOMETRY

LDPE morphology more affected by irradiation than HDPE: role of additives confirmed
CONCLUSION ON STERILIZATION EFFECT FOR LDPE

- Loss of volatiles induced by gamma irradiation: decrease of VOC and sVOC and decrease of weight loss after irradiation and extraction
- High increase of LCB especially at high MW (> $10^5$ g.mol$^{-1}$)
- Broader MWD after irradiation and increased content of high MW polymers

Why high MW seems more affected?

Probability of a radical recombining with a high MW species vs low MW species is much higher

CONCLUSION ON STERILIZATION EFFECT FOR HDPE

Irradiation increases VOC & sVOC but decreases nVOC
• Additives degradation from nVOC to VOC (no difference in weight loss before vs after)

Broader MWD after irradiation and increased content of high MW polymers
• Increase of LCB especially at high MW
• Effect less pronounced than LDPE (additive free): antioxidants prevent degradation

Yellowing occurred after irradiation
• Additive decomposition product suspected

* Crosslinking between 2 polymers
* Increases both LCB and MW
* If not prevented, can adversely affect HDPE properties

CONCLUSION

Study of impact of solvent (polarity, pH), analysis, LOD
- Set-up of analytical conditions, solvents, thresholds
  Hexane (1 ppm), EtOH (1 ppm), UPW pH 7 (50 ppb)
  HS-GC-MS, GC-MS, LC-MS, weight loss, GPC
- Extractables studies performed on several SABIC Healthcare grades

Study on impact of $\gamma$-Sterilization on HDPE and LDPE
- Impact on extractables, Molecular weight distribution
- Crosslinking and long chain branching observed after $\gamma$-treatment
- Additives in HDPE reduces sterilization impact on material properties

SABIC has developed an increased level of understanding of Healthcare industry for a better service and support
THANK YOU FOR YOUR ATTENTION
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