Multilayer Plastic Vial & Syringe with Excellent Oxygen Barrier

Researcher
Haruka Okazaki

MITSUBISHI GAS CHEMICAL
Mitsubishi Gas Chemical (MGC)

- Belonging to Mitsubishi Group
- Head Office: Tokyo, Japan
- Established in Jan.1918
- Net Sales: US$ 5.5 billion
  (On a Consolidated basis, Mar. 2017, US$1=¥100)
- Employees: approx. 8000
  (On a Consolidated basis, Mar. 2017)
- Main Products
  - Methanol
  - Hydrogen Peroxide
  - Polycarbonate
  - Nylon-MXD6
  - Oxygen Absorber (AGELESS®)
  - etc.

Overseas:
5 sales offices, 19 productions

Japan:
2 sales offices, 7 productions,
3 research centers
Nylon-MXD6

• **Polyamide Resin**

\[
\begin{align*}
\text{H} & \text{NHCH}_2 \text{CH}_2 \text{NHCO} \text{(CH}_2\text{)}_4 \text{CO} \text{OH} \\
\text{n}
\end{align*}
\]

• **Features**
  - Good Gas-Barrier (O\(_2\), CO\(_2\), etc.)

• **Applications**
  - Injection Blow Molding
    - Soda Bottles
    - Beer Bottles
  - Extrusion Molding
    - Food Packaging
• **Sachet Type of Oxygen Absorber**
  
  • **Features**
    - Prevents oxidation
    - Preserves flavor and nutrition
  
  • **Applications**
    - Used in Gas-barrier packaging

**MGC** is a leading company in the field of oxygen barrier material and oxygen absorber.
Today’s Overview

✓ Features of Glass and Plastics
   ~ Various good aspects of Plastics ~

✓ Excellent Oxygen and
   Water Vapor Barrier Ability of OXYCAPT™

✓ Concept of OXYCAPT™
   ~ Two key technologies;
      New Oxygen Absorbing Resin
      & Multilayer Configuration ~

✓ Technical Data of OXYCAPT™
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## Glass vs Plastics

<table>
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<tr>
<th></th>
<th>Glass</th>
<th>Plastics (COP) ※Cyclo Olefin Polymer</th>
</tr>
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<tbody>
<tr>
<td><strong>Oxygen Barrier</strong></td>
<td>Excellent (Permeation = Zero)</td>
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</tr>
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<td>Poor</td>
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</tr>
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<td><strong>Transparency</strong></td>
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✓ Technical Data of OXYCAPT™
MGC has developed a new plastic medical container with excellent oxygen and water vapor barrier.
**OXYCAPT™** has the best properties both of Glass and Plastics container.

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OXYCAPT™ Technology

New Oxygen Absorbing Resin

- Excellent Oxygen Barrier
- Retains Strength
- Low Extractables

Oxygen Permeability (cc·mm/m²/atm/day) vs. Time (Day)

- PET
- Amorphous Polyamide
- New Oxygen Absorbing Resin

Multilayer Configuration

- Improves the properties
- Co-injection molding

OXYCAPT™ Vial & Syringe

- Plastic containers with excellent oxygen barrier
- Suitable for oxygen sensitive drugs
Oxygen absorbing resin has excellent oxygen barrier as it absorbs oxygen from outside.

**Passive Barrier Resin**
- Outside: $O_2$
- Inside: $O_2$
- Permeation

**Oxygen Absorbing Resin**
- Outside: $O_2$
- Inside: $O_2$

attack contents

Oxygen absorbing
**Existing oxygen absorbing resins’ **problems

- High levels of low-molecular-weight extractables
- Lose structural strength

**Example 1.** The oxidation of **ether** with transition metal

\[
\text{O}_2 + \text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{O} \rightarrow \text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{O} + \text{HO}_2^-
\]

**Example 2.** The oxidation of **butadiene** with transition metal

\[
\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2 \rightarrow \text{CH}=\cdot + \text{HO}_2^- + \text{CH}_2=\text{CH}_2 + \text{CH}_2=\text{CH}_2
\]

**Degradation!**

Existing OA resins’ film after oxygen absorbing
New Oxygen Absorbing Resin

~Does not Degrade~

~Retain Strength~

~Low Extractables~

<Tensile Strength Test>

- Sample: The 10mm wide film.
- Measurement device: tensile testing machine

<TOC Analysis>

The films (SA: 200cm²) were soaked in 100mL water and stored for 1 week at 60°C
OXYCAPT™ has advantages of both new oxygen absorbing resin and COP, and achieves glass-like gas barrier!
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Features of OXYCAPT™ Vial & Syringe

<Features>
- Excellent Oxygen Barrier
- Excellent Water Vapor Barrier
- Extremely Low Extractables
- Low Protein Adsorption
- High Transparency
- High Breakage Resistance
- Good pH Stability
- Easier Disposal than Glass
- Much Lighter than Glass

Nest & Tab
OXYCAPT™ has excellent oxygen barrier, and can protect drugs just like glass.

### Oxygen Permeability

**10ml Vial**

- **COP**
- **COP/PA**
- **Glass**
- **OXYCAPT™**

**Oxygen Permeability**

- **Closure**
- **Vial body**

**1mL Long Syringe**

- **Stopper**
- **Barrel wall**
- **Tip Cap**

**Oxygen Permeability from barrel ÷ ZERO**

- **COP**
- **Glass**
- **OXYCAPT™**

- Extremely low (Over 100 times better than COP)

- Measurement device: MOCON OX-TRAN® 2/61
- Condition: 23°C / In 100%RH, Out 50%RH

Similar to Glass
OXYCAPT™ keeps excellent oxygen barrier like glass.
**OXYCAPT™ keeps Zero oxygen concentration in its headspace just like glass for a long time.**

**Test method**
- Filled with 5mL water
- Freeze degassing
  - $N_2$ gas introduction
  - Freeze degassing again
  - Zero oxygen concentration in headspace
- Stored at 25°C • 60%RH
- Analysis; oxygen analyzer

![Diagram of oxygen concentration in headspace over storage period](image-url)

- Graph showing concentration of oxygen [%] over storage period [day] for different materials:
  - Glass
  - COP
  - OXYCAPT™

---

*O₂* Headspace (Zero oxygen concentration)
OXYCAPT™ has excellent water vapor barrier like COP.

Water Vapor Permeability

<table>
<thead>
<tr>
<th></th>
<th>10ml Vial</th>
<th>1ml Long Syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>[Diagram]</td>
<td>COP: [Diagram]</td>
</tr>
<tr>
<td>COP</td>
<td>[Diagram]</td>
<td>OXYCAPT™: [Diagram]</td>
</tr>
<tr>
<td>OXYCAPT™</td>
<td>[Diagram]</td>
<td>COP: [Diagram]</td>
</tr>
</tbody>
</table>

Similar To COP

measurement device: MOCON PERMATRAN-W® 3/33
Condition: 40°C / In 100%RH, Out 5%RH
Organic Extractables

OXYCAPT™ has low organic extractables like COP.

<Test method>
- Filled with 100mL water
- Stored for 3 month at 40℃
- Analysis; TOC

OXYCAPT™ 100mL Vial

TOC: Total Organic Carbon
Extractable Study

Extractables from OXYCAPTTM are same to that from COP.

**<Test method>**
- GC-MS and LC-UV-MS
- **6 solvents** recommended by *BioPhorum Operations Group* were selected.
  - 6 solvents: DI water, 50% Ethanol, 1% PS-80, 5M NaCl, 0.5M NaOH, 0.1M H₃PO₄
  - Prepared 2mL-solvents were put in vials and stored at 40°C, 25%RH for 70 days.
  - The duration is necessary to support 3 year storage time at 0 °C.

<table>
<thead>
<tr>
<th>Materials</th>
<th>Solvent</th>
<th>GC-MS (for volatile impurity)</th>
<th>LC-UV-MS (for non-volatile impurity)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Glass</em></td>
<td>DI water</td>
<td><em>Not detected</em></td>
<td><em>Not detected</em></td>
</tr>
<tr>
<td></td>
<td>50% Ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>COP</em></td>
<td>DI water</td>
<td><em>Not detected</em></td>
<td><em>Not detected</em></td>
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<tr>
<td></td>
<td>50% Ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1% PS-80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5M NaCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5N NaOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1M Phosphoric acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>OXYCAPT</em></td>
<td>DI water</td>
<td><em>Not detected</em></td>
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<td>0.1M Phosphoric acid</td>
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</table>

-The studies were conducted by American CRO, Frontage Laboratories, Inc.(Exton, PA).
Elemental impurity

Extractables from OXYCAPT™ are same to that from COP.

<Test method>
- ICP-MS
- 1% HNO₃ recommended by CRO was selected

*These elements were selected based on ICH Q3D.

OXYCAPT is suited to medical containers.
**OXYCAPT™ shields UV light below 300nm.**

⇒ **OXYCAPT™** vial can protect UV-sensitive drug.
Protein Adsorption

**OXYCAPT™ has low protein adsorption, reducing unwanted residues of protein.**

**Test method**

1. 5wt% albumin solution was put into vials and stored for 24h.
2. Dyed with “Coomassie brilliant blue R-250” solution for 6h.
3. Rinsed with methanol 4 times.

Deeper Blue = more protein residue.
Laminated Stopper for OXYCAPT™ Syringe

<Components of OXYCAPT™ Syringe>

- OXYCAPT™ Syringe barrel
  - Silicone-free

- Stopper
  - PTFE-laminated butyl rubber

<Feature of laminated stopper>

- Slight silicone-coat or Silicone-Free
- Light break-loose and gliding force
- Low extractables
- Meet JP, EP, USP requirement
  - JP 7.03/EP 3.2.9./USP <381>
- Sterilized by ETO
- Inspection of endotoxin and bioburden
Gliding Force of OXYCAPT™ Syringe

OXYCAPT™ syringe can minimize silicone oil and decrease the break-loose force and glide force.

<Test method>
- 1 mL long Syringe
  (27G × 1” needle was attached)
- Filled with 1mL distilled water
- Stroke device : INSTRON® 5967
- Stroke rate : 200 mm/min

※Gliding force increases gradually due to its inner draft angle.
Sample Availability

Sample supplying has been started. If requested, custom-made containers are available.

(10mL Vial for initial evaluation)

(1mL Long Syringe for initial evaluation)

<table>
<thead>
<tr>
<th>Type</th>
<th>Size</th>
<th>Sample Supply</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial</td>
<td>2mL</td>
<td>From April 2018</td>
<td>ISO 8362-1</td>
</tr>
<tr>
<td></td>
<td>6mL</td>
<td>Already started</td>
<td>ISO 8362-1</td>
</tr>
<tr>
<td></td>
<td>10mL</td>
<td>Already started</td>
<td>ISO 8362-1</td>
</tr>
<tr>
<td>Syringe</td>
<td>1mL Long</td>
<td>Already started</td>
<td>ISO 11040-6</td>
</tr>
<tr>
<td></td>
<td>2.25mL</td>
<td>Already started</td>
<td>ISO 11040-6</td>
</tr>
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</table>

※Sterilized by gamma-ray.
※These samples are trial products, not guaranteed.
※Only for compatibility testing (e.g. 6 months storage)
# Regulatory Compliance

Regulatory works of bulk vial are expected to be completed by 4Q 2017. All regulatory works are expected to be completed by 2Q 2018.

<table>
<thead>
<tr>
<th>Product</th>
<th>Area</th>
<th>Requirement</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxygen Absorbing Resin</strong></td>
<td>USA</td>
<td>USP 661.1 (Physicochemical)</td>
<td>Meet Requirements</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>USP 87/88 (Biological Test)</td>
<td>Meet Requirements</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>Drug Master File</td>
<td>No.27495</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>EU-Directive (PIM)</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>EP (for Polyolefin)</td>
<td>Meet Requirements</td>
</tr>
<tr>
<td><strong>COP</strong></td>
<td>Japan</td>
<td>JP7.02 (as Container)</td>
<td>Meet Requirements</td>
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<tr>
<td></td>
<td>USA</td>
<td>Drug Master File</td>
<td>No.14084 &amp; 27657</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>EP (for Polyolefin)</td>
<td>Meet Requirements</td>
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<td><strong>Vial</strong></td>
<td>Japan</td>
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<tr>
<td></td>
<td>USA</td>
<td>USP661.2</td>
<td>In Progress (expected to be completed by 4Q 2017)</td>
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<tr>
<td></td>
<td>USA</td>
<td>USP671</td>
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<td>No.30669</td>
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<tr>
<td></td>
<td>Europe</td>
<td>EP3.2.2.1</td>
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<tr>
<td><strong>Syringe</strong></td>
<td>Japan</td>
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<td>-</td>
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MGC has developed "OXYCAPT™ Vial & Syringe" for bio drugs.

OXYCAPT™ Vial & Syringe have greatest features of both Glass and Plastics.
Glass-Like oxygen and water vapor barrier,
Low levels of inorganic and organic extractables,
Low protein adsorption,
High resistance to breakage, etc.

Custom-made OXYCAPT™ containers are available.
Thank you for listening.

MGC’s booth number is 42D71.
We are looking forward to meeting you at our booth.