MITSUBISHI GAS CHEMICAL

UPDATE ON OXYCAPT MULTILAYER PLASTIC VIAL AND SYRINGE

Here, Tomohiro Suzuki, Associate General Manager at Mitsubishi Gas Chemical Company, gives an update, including new oxygen barrier data, on the development of the OXYCAPT™ multilayer plastic vial and syringe.

Mitsubishi Gas Chemical (MGC) is one of Mitsubishi's companies and one of the leaders in the field of oxygen barrier and absorbing technologies. Our special polymer, Nylon-MXD6, has been used for the middle layer of multilayer beverage bottles for many years to prevent oxidation and carbon dioxide evaporation. Also, our oxygen absorber AGELESS has been used for more than 30 years for intravenous solutions and prefilled syringes to prevent oxidation of injectable drugs.

> "Although about 70% of UV light of 300 nm transmits through glass and COP, only 1.7% of UV light transmits through OXYCAPT."

Based on these technologies and experiences, we have developed a multilayer plastic vial and syringe called OXYCAPT (Figure 1). It consists of three layers – the drug contact layer and the outer layer are made of cyclo-olefin polymer (COP), and the oxygen barrier layer is made of our novel polyester (Figure 2). OXYCAPT possesses excellent oxygen barrier, high water vapour barrier and ultraviolet (UV) barrier properties, very low extractables, high pH stability, low protein adsorption and aggregation, a silicone-oil free barrel, high transparency, high break resistance, easier disposability and lighter weight.

Figure 1: The OXYCAPT multilayer plastic vial and syringe.

Tomohiro Suzuki
Associate General Manager
T: +81 3 3283 4913
E: tomohiro-suzuki@mgc.co.jp

Mitsubishi Gas Chemical Company
Mitsubishi Building
5-2 Marunouchi 2
Chiyoda-ku
Tokyo 100-8324
Japan

www.mgc.co.jp/eng

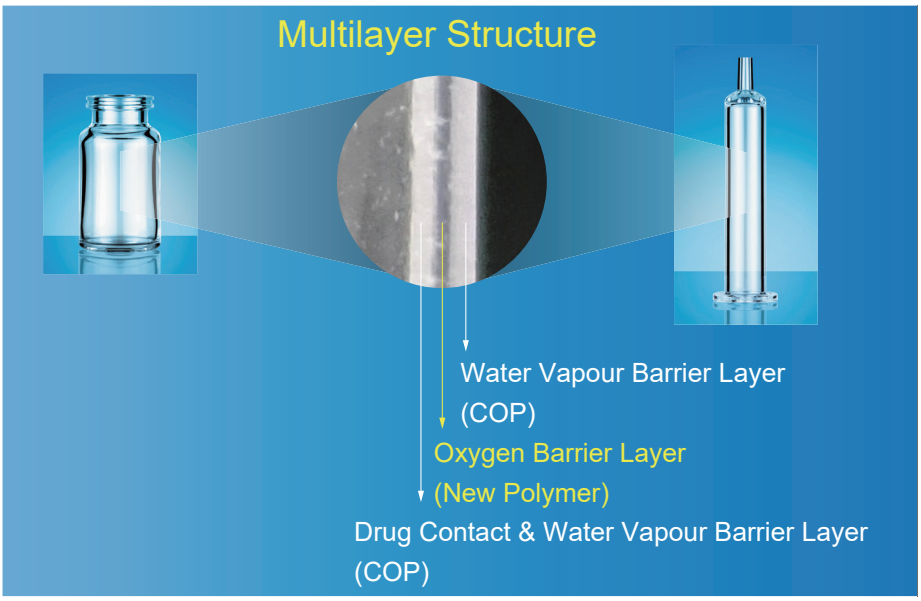


Figure 2: The multilayer structure.

There are two types of OXYCAPT multilayer plastic vial and syringe – OXYCAPT-A and OXYCAPT-P. OXYCAPT-A has achieved a glass-like oxygen barrier (Table 1). According to some internal studies, thanks to its oxygen absorbing function, OXYCAPT-A can maintain lower oxygen concentrations in the headspace than Type 1 glass. OXYCAPT-P has also achieved an excellent oxygen barrier, although there is no oxygen absorbing function. For example, the oxygen barrier of the OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial. OXYCAPT-A is particularly suitable for oxygen-sensitive drugs and OXYCAPT-P is recommended for all drugs.

OXYCAPT is an excellent UV barrier. Although about 70% of UV light of 300 nm transmits through glass and COP, only 1.7% of UV light transmits through OXYCAPT (Table 2). We have confirmed this feature also contributes to the stability of biologics.

Regarding the water vapour barrier, OXYCAPT cannot reach the performance of glass. However, it is similar to COP, which has been used for injectable drugs for a long time, and easily meets the requirements of a water vapour barrier in ICH guidelines.

"The OXYCAPT syringe consists of a tip cap, a barrel, a polytetrafluoroethylene-laminated stopper and a plunger rod."

"The OXYCAPT vial and syringe are produced by co-injection moulding technology."

Studies have shown extremely low extractables from OXYCAPT. One study was conducted to confirm volatile, semi-volatile and non-volatile impurities from OXYCAPT. Water and four solutions (50% ethanol, NaCl, NaOH and H_3PO_4) were selected, and impurities were measured by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the blank, impurities were not detected in OXYCAPT containers. A second study confirmed that inorganic extractables levels from OXYCAPT were

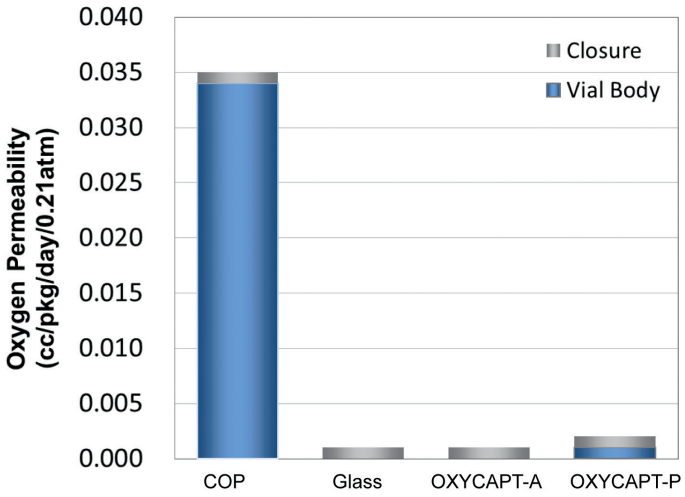


Table 1: Graph of oxygen barrier.

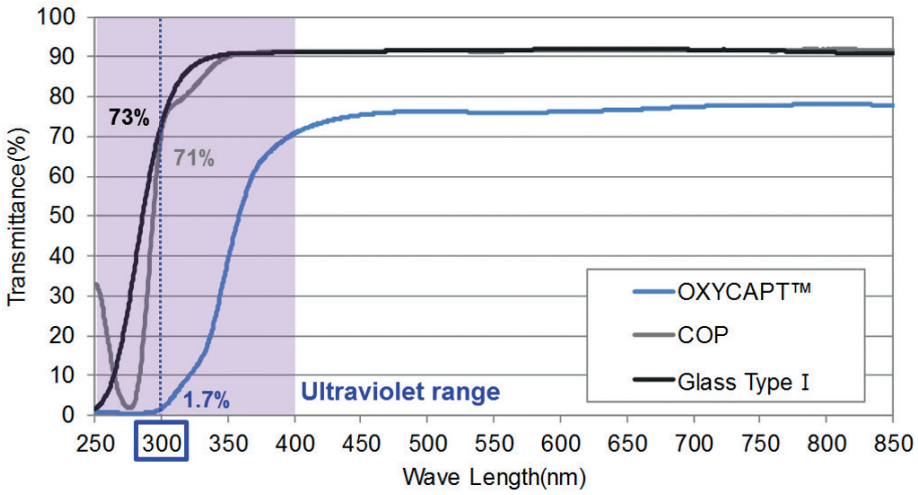


Table 2: Graph of ultraviolet barrier.

"We are the first company that has succeeded in developing multilayer plastic syringes."

similar to those from COP, which is well known as an extremely pure polymer, and with a better extractables profile than Type 1 glass. Lower levels of inorganic extractables are known to contributes to better pH stability in drug products (Table 3).

The OXYCAPT syringe consists of a tip cap, a barrel, a polytetrafluoroethylene-laminated stopper and a plunger rod. Although a very small amount of silicone oil is sprayed on the stoppers of OXYCAPT syringes, no silicone oil is baked on the barrel. According to our internal studies using existing antibodies, we have found this feature leads to much less protein aggregation compared with existing Type 1 glass syringes.

The OXYCAPT vial and syringe are produced by co-injection moulding technology. Although this technology has been applied to beverage bottles for many years, we are the first company that has succeeded in developing multilayer plastic syringes. We have also developed the inspection methods for the oxygen barrier layer. All the containers are 100% inspected by state-of-the-art machinery.

MGC can offer bulk vial, ready-to-use (RTU) vial and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO-based nest and tub formats (Figure 3). The nest and tub are mainly sterilised by gamma ray. There are 2 mL, 6 mL, 10 mL and 20 mL for vials, and 1 mL long and 2.25 mL for syringes

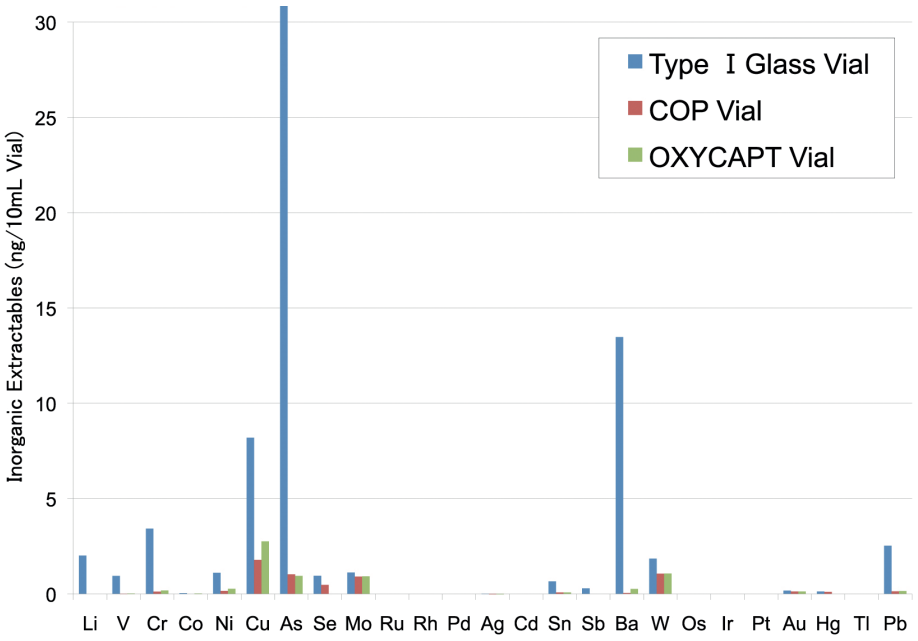


Table 3: Graph of inorganic extractables.

Figure 3: The nest and tub.

(Table 4). We are willing to provide samples for initial testing free of charge.

Each polymer meets the requirements of USP 661, USP87, USP88, EP, and has been filed in the US FDA's drug master file (DMF). The vials and syringes are also compliant with each pharmacopoeia and have been filed in the DMF. The syringes are produced and controlled in accordance with ISO 13485.

Type	Volume	ISO	Parts	Option
Vial	2 mL	ISO 8362-1	Vial	Bulk or RTU
	6 mL	ISO 8362-1	Vial	Bulk or RTU
	10 mL	ISO 8362-1	Vial	Bulk or RTU
	20 mL	ISO 8362-1	Vial	Bulk or RTU
Syringe	1 mL Long	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU
	2.25 mL	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU

Table 4: Product portfolio.

COLD STORAGE RESISTANCE

We have conducted some studies of cold-storage resistance. OXYCAPT vials and a competitor's COP monolayer vials were stored at approximately -180°C in a gas phase of liquid nitrogen, and then dropped from a height of 150 cm. Although some COP monolayer vials were broken, no breakage was observed in the OXYCAPT vials (Figure 4). As liquid nitrogen storage has become popular, thanks to the spread of regenerative medicine, OXYCAPT is expected to be used for this new field.

Finally, we would like to share some of our latest data. We are often asked if the oxygen barrier of OXYCAPT-A is better than Type 1 glass or not. In addition, some customers have informed us that the oxygen barrier of COP must be improved at lower temperatures. To answer such questions, we measured oxygen concentration in vials after storage at 25°C and 5°C. We confirmed that the oxygen concentration of OXYCAPT-A was better than that of Type 1 glass at 25°C (Figure 5). Also, we found that the oxygen concentration in COP vials at 5°C climbed to 10% after four months' storage and OXYCAPT-A and -P could maintain very low oxygen concentrations at both 25°C and 5°C (Figure 6).

In conclusion, OXYCAPT has been developed to overcome some of the current problems conventional PFS face, and to meet unmet needs in the pharmaceutical industry. In addition to special features of COP such as a high water vapour barrier, high break resistance, very low extractables and low protein adsorption, OXYCAPT can offer a high oxygen and UV barrier. We believe OXYCAPT brings considerable benefits, not only to improve product performance but also to achieve meaningful product differentiation, in the rapidly growing pharma industry.

ABOUT THE COMPANY

Mitsubishi Gas Chemical (MGC) does business in a wide range of fields, from basic chemicals to fine chemicals and functional materials. MGC established its advanced business development division in 2012 as a centre for creating new businesses, and has developed the OXYCAPT plastic vial and syringe as an alternative to glass containers.

ABOUT THE AUTHOR

Tomohiro Suzuki joined Mitsubishi Gas Chemical in 1998. He worked in the oxygen absorbers division until 2011 before moving to the advanced business development division in 2012 to be a member of the OXYCAPT development team. Since then, he has been in charge of the marketing of the OXYCAPT plastic vial and syringe.

OXYCAPT™ Vial is more durable than COP Vial at cryogenic temperature .

Samples and Test Methods

- Number of vial: 20 (OXYCAPT™-A 10 mL vial)
- Closure: brominated butyl rubber with aluminum seal
- Filled with 10 mL distilled water
- Stored: approximately -180°C (liquid nitrogen gas phase)
- Extremely frozen vials were dropped to a steel plate from 150 cm

Test Results

Number of Breakage	
OXYCAPT™-A Vial	COP Vial
0/20	8/20

Broken COP Vial

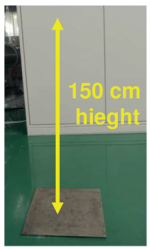
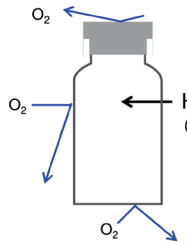


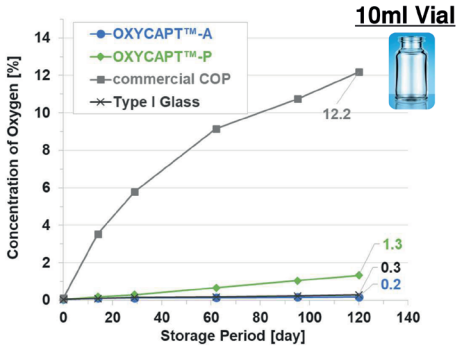
Figure 4: Break resistance at cryogenic temperature.

OXYCAPT™-A keeps better oxygen barrier than glass.
OXYCAPT™-P keeps much better oxygen barrier than COP.

Test sample
- OXYCAPT™-A & -P 10 mL vial
- Butyl rubber closure with aluminium seal

Test method
- Initial oxygen concentration: 0%
- Stored at 25℃ ・ 60%RH
- Analysis; oxygen analyzer





Calculated Oxygen Concentration after 2 years

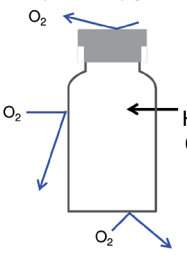
OXYCAPT-A	OXYCAPT-P	COP	Glass
0.7%	7.7%	21.0%	1.5%

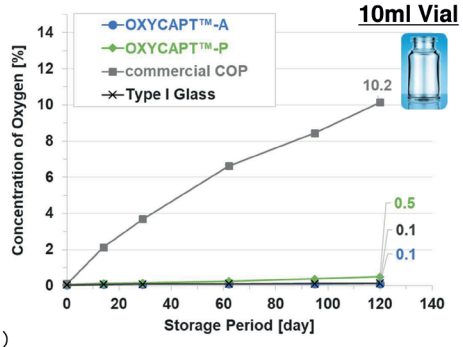
Figure 5: Oxygen concentration at 25°C.

OXYCAPT™-A keeps better oxygen barrier than glass.
OXYCAPT™-P keeps much better oxygen barrier than COP.

Test sample
- OXYCAPT™-A & -P 10 mL vial
- Butyl rubber closure with aluminium seal

Test method
- Initial oxygen concentration: 0%
- Stored at 5℃
- Analysis; oxygen analyser





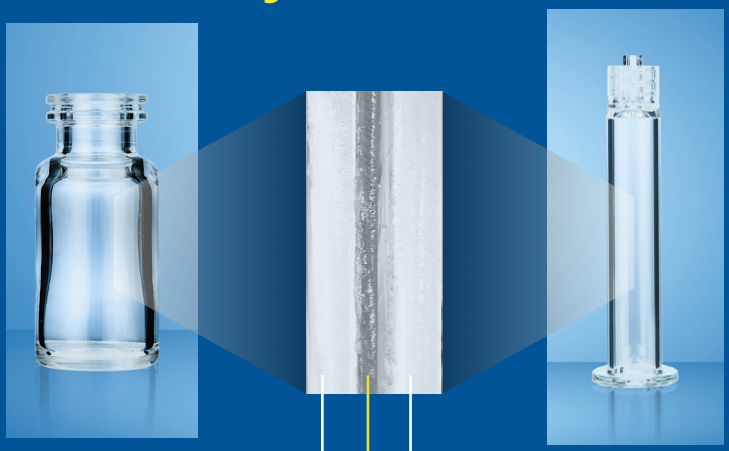
Calculated Oxygen Concentration after 2 years

OXYCAPT-A	OXYCAPT-P	COP	Glass
0.4%	2.6%	21.0%	0.5%

Figure 6: Oxygen concentration at 5°C.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
- Customizable
- For Biologics & Regenerative Medicine

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