

Why devices are failing in oncology drug delivery applications

The new challenges of chemical resistance and FDA regulations

Advanced oncology drugs and carrier solvents challenge the chemical resistance of polymers used in delivery devices.

Some oncology chemotherapies—the cancer drugs as well as the carrier solvents that help them work effectively—are not compatible with traditional polymers used in delivery devices.

Such conditions can prevent the devices from properly doing their job—or cause them to fail prematurely. When there is a pattern of compromised device performance or life cycle, regulatory agencies may tell manufacturers to stop using certain materials to protect the well-being of patients.

The stakes are critically high.

Device manufacturers have more reasons than ever to understand the chemical resistance of the materials they use in devices, including the following.

1. The widespread use and economic importance of oncology drugs

- Worldwide spending on cancer treatments reached **\$100 billion**¹ in 2014.²
 - Up 10.3% from 2013 to 2014
 - Up 33% since 2009
- Between 2012 and 2013, out-of-pocket costs for **IV cancer drugs grew by 71%** (oral drugs grew by 16%).²
- U.S. **per capita spending** on oncology drugs reached \$99 in 2014—up from \$71 in 2010.²
- U.S. spending accounted for 42% of worldwide spending.²
- Cancer care costs are rising faster than overall health care costs.³
- **Eight of the ten most expensive drugs** are oncology drugs.³
- As a class, oncologics account for greater spending worldwide than any other therapy area—outpacing antidiabetics by 17% and pain therapies by nearly 25%.⁴

¹ Including therapeutic treatments and supportive care and exclusive of discounts, rebates, and price reductions related to patient access programs

² Developments in Cancer Treatments, Market Dynamics, Patient Access and Value. *Global Oncology Trend Report 2015*. IMS Institute for Healthcare Informatics. May 2015.

³ 2014 Cancer Center Business Summit. Available at: <http://www.imshealth.com/portal/site/imshealth>. Accessed May 2014.

⁴ Top 20 Therapeutic Classes, 2014. IMS Health website. Available at: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/Top_line_data/2014/Top_20_Global_Therapy_Classes_2014.pdf. Accessed 12 Oct. 2015.

⁵ FDA MedWatch email, 10 Mar. 2015. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm437626.htm>. Accessed 10 Oct. 2015.

You will learn ...

- ➔ *The growing therapeutic and economic importance of oncology drug therapy*
- ➔ *The implications of the 2015 FDA Safety Alert for oncology drug devices*
- ➔ *How engineering polymers compare for compatibility with oncology drugs and carrier solvents*

2. A recent FDA Safety Alert⁵ concerning infusion devices made with polycarbonate (PC) or acrylonitrile butadiene styrene (ABS)

In March 2015, the FDA and the Institute for Safe Medication Practices (ISMP) issued warnings to health care professionals to stop using the chemotherapy drug bendamustine (Treanda, Teva Pharmaceutical Industries) with closed-system transfer devices (CSTDs), adapters, and syringes containing PC or ABS.

See inside for details behind these warnings and their implications for chemical resistance in cancer drug delivery devices.



Understanding chemical resistance can inform polymer selection.

Engineering polymers offer many advantages for infusion and blood contact devices compared with other materials.

Advantages include design and color flexibility, aesthetic appeal, reduced weight, corrosion resistance, and clarity.

But polymers that have a low level of compatibility with chemicals such as lipids, disinfectants, and specific oncology drugs and solvents can experience environmental stress cracking (ESC) or premature device failure in the presence of applied or residual stress.

With the goal of improved patient safety, all stakeholders can help reduce the risks of product failure—and help find safe alternatives—through:

- Vigilance by regulatory agencies
- Chemical resistance research by polymer manufacturers
- Informed polymer selection for oncology drug delivery devices

Evaluating polymers for chemical resistance

If DMAc is incompatible with PC and ABS, what about other carrier solvents? What about the oncology drugs themselves? Are there polymer alternatives that offer greater chemical resistance?

These are some of the questions Eastman wanted to answer with a series of chemical resistance tests. Testing recognized that chemical resistance involves more than chemical compatibility—so it measures the ability of a material to withstand exposure to a chemical with the addition of stress. The process also considered these factors associated with chemical attack:

- Chemical concentration/exposure time
- Reduced energy required for disentanglement (solvation/plasticization)
- Reduced rigidity, clarity, and modulus
- Dynamic fatigue (cyclic loading)

Regulatory vigilance at work—the success story behind the FDA Safety Alert¹

- N, N-dimethylacetamide (DMAc) is a carrier solvent ingredient used in bendamustine as well as the cancer drugs amsacrine and busulfan².
- According to the FDA, devices that contain PC and ABS dissolve when they come in contact with DMAc.
- This incompatibility in oncology drug delivery devices can pose serious risks, including:
 - Leaking
 - Breaking
 - Operational failure of the CSTD components
 - Possible contamination of the drug
 - Potential adverse health consequences to practitioners (skin reactions)
 - Potential adverse consequences to patients if dissolved PC or ABS enters the patient's vascular system
- The FDA continues to provide updates about compatibility.

¹ FDA MedWatch 10 Mar. 2015 (updated 4 Sept. 2015). Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm437626.htm>

² Pharmacy Practice News, ISSUE: APRIL 2015 | VOLUME: 42. "Chemotherapy May 'Melt' Some CSTDs." Available at: http://pharmacypracticenews.com/ViewArticle.aspx?d=Clinical&d_id=50&i=April+2015&i_id=1165&a_id=31083. Accessed November 4, 2015.

Methods

- Eastman used a modified ASTM D543 test for evaluating chemical resistance.
- Tests compared flex bar samples molded from PC, impact modified styrenic, and Eastman Tritan™ copolyester.
- Samples were exposed to various oncology drugs and carrier solvent chemicals for 24 hours while being held under 1.5% strain.
- After exposure, the samples were impacted with a pendulum hammer to measure the energy required to break them.

Step 1 1/8" x 0.5" x 5" polymer bar



Step 2 1.5% strain, 24 h chemical exposure



Step 3 Measure impact energy to break.



Table 1—Residual property evaluation: Impact properties against oncology drug carrier solvents

Materials	Control (joules)	MCT oil ^a	Etoposide carrier solvent ^b	Busulfex [®] carrier solvent ^c	Dimethylacetamide	Dimethyl sulfoxide
		% Retention of impact energy to break				
Tritan MX711 (standard)	4.4	68 ± 13	90 ± 2	79 ± 6	63 ± 35	84 ± 2
Tritan MX731 (high flow)	4.3	33 ± 2	78 ± 23	39 ± 8	25 ± 15	60 ± 7
Polycarbonate (high flow)	5.3	7 ^d	All broke on jig.	All broke on jig.	All broke on jig.	All broke on jig.
Polycarbonate (standard)	5.4	34 ^d	12 ± 1	All broke on jig.	All broke on jig.	All broke on jig.
Polycarbonate (lipid resistant)	5.5	47 ± 52	28 ± 42	All broke on jig.	All broke on jig.	All broke on jig.
Impact modified styrenic	4.3	10 ± 1	7 ^e	6 ± 1 ^f	Severe surface attack	9 ^e

■ > 80% retention ■ > 60% retention ■ < 60% retention

^aMCT oil: medium chain triglycerides oil

^bEtoposide carrier solvent: 10 mL of the solvent mix contains 3.05 mL ethanol, 6.5 g of polyethylene glycol 300, 0.8 g polysorbate 80, 0.33 g benzyl alcohol, and 20 mg citric acid.

^cBusulfex injection carrier solvent: 10 mL of the solvent mix contains 3.3 mL dimethylacetamide and 6.7 mL polyethylene glycol 400.

^d3 of 4 samples broke on jig. Standard deviation not calculated.

^e2 of 4 samples broke on jig. Standard deviation not calculated.

^f1 of 4 samples broke on jig.

Results—against oncology drug carrier solvents

- Table 1 shows the results of exposure to DMAc (the solvent implicated in the FDA Safety Alert) and four other common solvents.

- All solvents were very aggressive on the engineered polymers.
- Grades of Tritan offered a higher level of property retention.
- Tritan MX711 offers significantly better chemical resistance compared to PC and impact modified styrenic, which is chemically similar to ABS.

Table 2—Residual property evaluation: Impact properties against oncology drugs

Materials	Control (joules)	Taxol [®]	Etoposide	Ifex [®]	Methotrexate	Cyclophosphamide	Adriamycin [®]
		% Retention of impact energy to break					
Tritan MX711 (standard)	4.4	80 ± 4	84 ± 2	91 ± 1	103 ± 1	105 ± 1	94 ± 4
Tritan MX731 (high flow)	4.3	46 ± 1	87 ± 5	96 ± 3	105 ± 1	95 ± 2	107 ± 2
Polycarbonate (high flow)	5.3	All broke on jig.	48 ± 46	28 ± 43	54 ± 58	104 ± 2	101 ± 11
Polycarbonate (standard)	5.4	12 ^a	66 ± 44	87 ± 41	101 ± 1	114 ± 2	104 ± 3
Polycarbonate (lipid resistant)	5.5	43 ± 42	76 ± 34	94 ± 9	77 ± 41	109 ± 2	113 ± 2
Impact modified styrenic	4.3	All broke on jig.	4 ± 1	9 ± 1	100 ± 1	100 ± 1	10 ± 2

■ > 80% retention ■ > 60% retention ■ < 60% retention

^a2 of 4 samples broke on jig. Standard deviation was not calculated.

Reference: Chemical resistance advantages of Tritan copolyesters for medical—Oncology drug case study, ANTEC 2014, 1812

Results—against oncology drugs

- Table 2 shows the results of exposure to six popular oncology drugs.

- Generally, results were much better than in Table 1.
- Overall, grades of Tritan offered a higher level of chemical resistance.

Summary

Eastman Tritan™ copolyesters have good overall chemical resistance and provide an attractive alternative to PC or ABS for oncology drug delivery devices. For CSTDs and other infusion devices, Tritan can be a candidate for molding devices that are compliant with FDA and ISMP Safety Alerts.

To evaluate polymers for your specific FFU requirements, it's important to consider these results—as well as actual testing of articles molded for the intended application. Eastman technical specialists are prepared to help you early in your process to produce high quality medical devices.

For additional results of tests comparing compatibility with medical disinfectants and disinfectant wipes or color shifting after sterilization with EtO or gamma irradiation, contact 844.4TRITAN.

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It is the responsibility of the medical device manufacturer ("Manufacturer") to determine the suitability of all component parts and raw materials, including any Eastman product, used in its final product to ensure safety and compliance with requirements of the United States Food and Drug Administration (FDA) or other international regulatory agencies.

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