Examining the amount and form of silver release from antimicrobial medical devices

Eric M. Sussman, Priyanka Jayanti, Brendan J. Casey, and Benita J. Dair
Division of Biology, Chemistry and Materials Science, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, Office of Medical and Tobacco Products, U.S. Food and Drug Administration

Statement of Purpose: To reduce infection of medical devices, manufacturers have incorporated nanometer-scale silver (nAg) antimicrobial coatings[1] on devices such as wound dressings and catheters. While silver (Ag) has a long history of safe medical use, extensive *in vitro* research has identified conditions under which cytotoxicity from nAg is detected[1], and is therefore of concern.

As part of performing a risk assessment of the potential negative effects induced by nAg release from medical devices, exposure analysis is necessary so that the amount of silver and its physical form are known.

Here, we assessed potential leachables exposure by performing extraction experiments under various conditions, including some of which are described in International Standards Organization (ISO) 10993-12, which is used to evaluate the biocompatibility of medical devices. These extracts were analyzed by various methods in order to characterize the amount of Ag released and the form of the Ag (soluble or particulate).

The results demonstrate significant differences in the amount and form of Ag that are released among the medical devices tested.

Methods: Multiple Ag-containing medical devices that we purchased (three types of wound dressings labeled WD1, WD2 and WD3 and two types of catheters labeled Cat1 and Cat2) were incubated in various extract solutions (water, saline, 100% citrated human plasma) under multiple conditions (1 hour, 24 hours, 168 hours @ 37°C; 72 hours @ 50°C). Inductively coupled plasma mass spectrometry (ICP-MS) was used to determine the total amount of Ag which had leached from the devices. Dynamic light scattering (DLS), ultraviolet-visible light spectroscopy (UV-Vis), nanoparticle tracking analysis (NTA) and transmission electron microscopy (TEM) were utilized to characterize the physical structure of the particulates released from the devices. Field emission scanning electron microscopy (FESEM), and corresponding energy dispersive x-ray spectroscopy (EDS) were used to image and analyze the elemental composition of the surface of each medical device. Not all data are displayed here due to space considerations.

Results: FESEM (Figure 1A) revealed variability in the surface morphologies of Ag in various commercial devices. Some devices contained sub-100 nm Ag particles while others contained much larger particles or only small traces of Ag. The release of Ag into extract media was also strongly device- and extract medium dependent. Order-of-magnitude differences in these amounts existed between the various devices (Figure 1B). Strikingly, there was multi-modal confirmatory evidence of Ag nanoparticle release from only one of the devices (WD1), which was confirmed using TEM with an average measured particle size of 20 ± 6 nm.

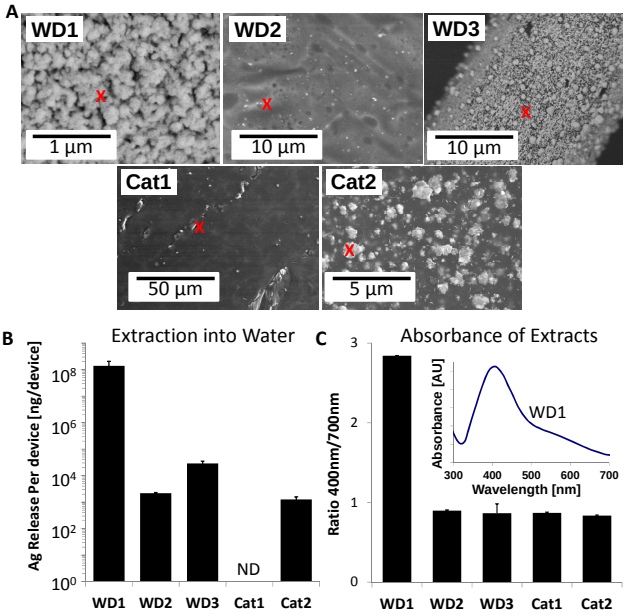

Figure 1. A) Field emission scanning electron microscopy of various Ag-containing medical devices (WD: wound dressing; Cat: catheter) reveals different Ag morphologies and energy dispersive x-ray spectroscopy indicated the presence of Ag (red X denotes location with highest Ag signal) **B**) Comparison of total amounts of Ag (soluble and particulate) in seven-day extracts of medical devices, based on the total size of the device (ND = none detected). **C**) Comparison of the absorbance of seven-day water extracts at 400 nm, the wavelength indicative of the presence of Ag nanoparticles due to the surface plasmon resonance effect. Only extracts of WD1 had measureable increases in absorbance at 400 nm (see inset).

Discussion and Conclusions: This study demonstrates that Ag-coated medical devices contain variable amounts and morphologies of Ag, and additionally, that the potential exposure in terms of the amount and form of Ag may be highly variable. Such exposure data is contributing to the development of risk assessments for nAg in medical devices.

References: [1]Maillard JY. Crit Rev Microbiol. 2012:39:373-83. *The authors acknowledge the FDA Nanotechnology Initiative for funding this research and the Oak Ridge Institute for Science and Education.*
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