

Document I:
SilvaSorb Site ® Dressing versus other silver containing site dressings such as SilverSite®.

Background: The SilverSite ® product brochure implies that when tested in a shake flask method, involving the immersion of site dressings into a nutrient broth containing pathogens, would result in superior performance of the SilverSite dressing compared to the SilvaSorb Site Dressing.

Additional features in the SilverSite Brochure states that the SilverSite product works instantly, with no need to wet dressing to activate.

Claims such as above need to be examined in the context of a reading of the concerned patents as well as data on file on SilvaSorb Site available at Medline.

Discussion: A reading of the patent number USP 6696077, that is cited in the SilverSite brochure, indicates that the SilverSite product contains as the active ingredient a chemical entity that is loosely described as a “silver alginate”. Leaving aside the fact that alginates in the wound dressing context are expected to be fibrous materials (for example Maxorb Ag ® is a silver alginate as commonly understood), one needs to further examine how this “silver alginate” is created. The silver alginate component in SilverSite is created by mixing sodium or calcium alginate with silver nitrate, a known cytotoxic agent (nitrate ions are cytotoxic) that is largely discontinued and shunned in clinical use. Other plasticizers and foaming agents are also used to prepare the final composition. The material also possibly contains colloidal silver.

During the manufacturing process, the “silver alginate” is not crosslinked via covalent bonds, but the mixture/paste created as described above is dried onto a substrate, for example on a polyurethane foam, to make the SilverSite product.

The problem with compositions such as the one described above is that they disintegrate quickly (not being crosslinked) in aqueous medium. While that could be advantageous in certain applications, as a wound dressing the dissolution of the dressing matrix is not desirable. For example, on a moist wound, the wound contact area of the SilverSite would turn into a jelly like purple substance, which would contain a large and possibly cytotoxic concentration of silver ions, plus also some cytotoxic nitrate ions. This disintegration effect of products such as SilverSite is easy to demonstrate by placing a drop of two of water or saline on the wound contact surface of SilverSite ® and gently rubbing this liquid into the product, this would be a realistic simulation of a site dressing that is shifting about in the application area in an environment with a few drops of body fluids present in the contact area. In a clinical environment, one has to then ask the question, is this purple paste evenly spread on the skin, and are the silver ions on which the product efficacy depends so clearly, evenly delivered and available on the skin?

The silver ion release associated with SilverSite is only limited by how much silver ions were loaded into the alginate polyanion during the manufacturing process through the introduction of the cytotoxic silver nitrate. There is no doubt that it is possible to deliver a large concentration of silver ions out of SilverSite.

However, the whole point of silver based dressings is to take advantage of the oligodynamic nature of silver, and delivering a possibly cytotoxic large dose of silver ions into a wound site rather defeats the point of having a silver dressing. The term “Oligodynamic” indicates that very small concentrations of silver ions, in parts per billion (ppb) level, are adequate for bioburden control in physiological environments. Many studies have thus shown that one only needs a small concentration of silver ions in a wound fluid to achieve elimination of pathogens present at realistic levels. Products such as SilvaSorb ® Site take advantage of the low solubility parameter of silver chloride, and thus limit themselves to a law of nature mandated silver concentration of about 1 ppm, a level which is proven safe and effective in wound care applications. Wound environments of course possess much higher bioburden levels typically compared to puncture sites, so a release level of 1 ppm is more than adequate for a puncture site wound.

Data on actual reduction of human skin bioburden would have been interesting to compare, but the SilverSite brochure does not comment on such test results on real human beings. The claim is made in the brochure that SilverSite “Works instantly, no need to wet dressing to activate”, however it is known in the field of alginate products that the silver ions can only be released out of the alginate polyanion complex when some other counterion (such as sodium in saline or nutrient broth, or in wound fluid) has replaced the silver ion in the “silver alginate”. It is very difficult to imagine such ion exchange happening without liquid water on largely intact skin. And if liquid/body fluid is present to effect ion exchange, the contact surface turns into a purple paste, not a desirable property in a skin contact device. Because of the requirement of fluid driven ion exchange, a conclusion one reaches is that around a dry puncture site, the SilverSite may not be active at all.

Real life testing on human skin has shown, on the other hand, that SilvaSorb Site reduces wound bioburden from 1, 370, 000000 to less than 40 in 24 hours. This type of testing is far more simulative of real life use than the testing done in an artificial environment shown in the SilverSite brochure. This human skin data on SilvaSorb Site is available on file. In contrast to the measured silver ion release from SilvaSorb Site, SilverSite delivers the components of the highly cytotoxic silver nitrate onto skin. To keep this in context, due to its toxicity profile, silver nitrate is a substance whose use on skin is no longer acceptable in current clinical environment. Also, one must remember that an insertion site is heavily “prepped” prior to device insertion, the skin bioburden can be reasonably assumed to be much lower than the worst case scenario 1.37 billion cfu’s that was tested on SilvaSorb Site, yet SilvaSorb Site managed that high bioburden without any problem.

The question of what happens to the cytotoxic nitrate ions that must remain in the product from the manufacturing process described in the patent on SilverSite is not clear. Silver ions are cytotoxic, specially in the high levels that is implicit in the reading of the cited patent on SilverSite, and there seems little benefit in adding further to the cytotoxicity by the additional presence of nitrate ions.

The zone of inhibition data available on the SilverSite product is curious and these may be artifacts of the experimental method used. Head to head testing of SilvaSorb Site and Biopatch through zone of inhibition measurements showed that the SilvaSorb Site product performed better than Biopatch, with consistent zones of inhibition extending from the boundary of the product. This data is available in TR-06-003 (Document . Testing is being re-performed to obtain confirmation of the data.

Conclusion: The important points to remember are:

1. Silver is oligodynamic. One only needs 1 ppm levels to achieve bioburden control. Levels above that are increasingly cytotoxic. The FDA requires testing data in shake flask methods which typically require a million cfu/ml germ concentration. Because of the deliberately controlled 1 ppm silver release level obtainable from SilvaSorb Site, it is always possible to concoct unrealistically high germ concentrations where the 1 ppm level of silver will not suffice. From the variable initial cfu/ml values which were chosen for various pathogens in the testing described in the SilverSite brochure, it seems that pathogen concentrations were deliberately sought out for testing where the 1 ppm silver levels would not be adequate for control.
2. The SilverSite product contains nitrate counterions, at least by a reading of the related patent. So through the use of SilverSite, one has delivered the components of silver nitrate to the skin, though no clinician in today’s age would conceivably put toxic silver nitrate onto skin, **specially on delicate pediatric skin.**
3. The SilverSite product likely requires body fluid mediated ion exchange to release silver ions and display antimicrobial effectiveness, SilvaSorb Site does not depend on such ion exchange to release silver. So SilvaSorb Site is the real “not required to be wet to be effective” dressing.
4. There is no data on bioburden control on human skin with SilverSite dressing. There is such data on SilvaSorb Site dressings. This data is far more representative of real life conditions on human skin than exposure of site dressings to pathogens in a test tube in a complete liquid environment.
5. The purple silver-containing zone of the SilvaSorb Site product will tend to disintegrate into a purple paste upon the slightest exposure to fluid. This paste is antimicrobial, but cannot be expected to be available uniformly at the puncture site, by the very nature and consistency of that

paste. One would really have been better off using the toxic silver nitrate solution to wipe the skin for bioburden control.

6. SilverSite is not translucent, requires lifting of the dressing to examine puncture site, adding trauma and further compromising the puncture site.
7. SilverSite is a sponge, so any fluid absorbed can be easily squeezed out, forming a pool under the dressing. Liquid absorbed by SilvaSorb Site cannot be squeezed out.