Sputter Synthesis of Antimicrobial Materials and Approaches to Optimization of the Process for Deposition on Web Substrates.

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Introduction

The ability of silver to guard against infection was already known in antiquity and, for example, silver containers were used for food storage and silver coins were dropped into water as a disinfectant. More recently, in 1884, Dr. Crede, a German obstetrician, used a 1% silver nitrate solution to prevent blindness in newborns caused by post-partum infection from syphilis infected mothers and, in 1887, Dr. von Behring used the same compound to treat typhoid and anthrax. Modern use of silver in wound treatment started in 1964 when Dr. Moyer of Washington University used silver nitrate to treat infection in major burn wounds. In 1968, Dr. Fox of Columbia University introduced silver sulfadiazine to medicine. The first sputtered nanocrystalline silver dressings were commercialized in 1998.

Silver attacks bacteria through multiple mechanisms. The bacterial cell wall is destabilized in the presence of silver which can cause it to break down and rupture, killing the bacterium. Silver can also find its way into the bacterial cell. There, it can interfere with the metabolic pathway responsible for cellular respiration, weakening or killing the bacterium. Silver will also inhibit replication of DNA, preventing bacteria from reproducing. This multiple action of silver is different from typical antibiotics, which generally work by interfering with a single metabolic pathway of a bacterium. For example, betalactams, such as penicillin, inhibit cell wall synthesis only, while flouroquinolones, such as ciprofloxacin, work uniquely by interfering with DNA synthesis. These varied attack mechanisms give silver a very broad spectrum activity, that is it fights infection from a wide range of different bacteria, and also reduces the probability that bacteria will develop resistance to silver, as they can often do with antibiotics. As such, silver is an excellent candidate to treat wounds which are, or run a serious risk of becoming, heavily infected by a wide variety of bacteria. Such wounds include serious burns and some chronic wounds.

Silver treatment using silver nitrate involves application of a solution soaked gauze. However, this leads to a very high concentration of silver in the wound, followed by a rapid drop as the silver is depleted due to both bacterial consumption and reaction with other constituents in the wound bed such as chlorine, phosphates, and proteins. Therefore, in order to maintain silver levels in the wound, frequent, painful dressing changes are required and silver levels in the wound are still highly variable. Furthermore, silver nitrate administrations are frequently hypotonic and therefore can cause strong electrolyte imbalances which can harm the wound site or, potentially, produce gross systemic imbalances which could even kill the patient. This is a particular concern in patients with large area burns that would require treatment with regular, large doses of silver nitrate.

Silver sulfadiazine was developed to try to overcome the shortcomings of silver nitrate and was expected to be particularly effective since both silver and sulfadiazine are known antimicrobials. It is applied in a cream format which needs frequent re-administration due to rapid silver depletion. Unfortunately, removal of the expended cream from the previous administration is often by scraping, which may cause considerable discomfort and detriment to the patient. Hypotonicity is not known to be an issue with silver sulfadiazine.

Sputtered Nanocrystalline Silver

Given the disadvantages of the above silver treatments, it would seem that there should be a better way of delivering silver. A better silver treatment would consistently deliver an appropriate level of active silver in a wound for a prolonged period, be effective against a broad range of bacteria, not interfere with the wound healing process and require limited dressing changes which would involve minimal disruption to the wound bed.

In the 1990's, extensive research was done on various ways to synthesize a silver coating to meet such criteria. Eventually, sputtering proved to be capable of producing a silver-based, nanocrystalline coating with the right characteristics. In contact with a moist wound the coating releases silver to levels sufficient to kill bacteria and maintains levels approximately constant for up to a week and beyond. The coating material can kill bacteria 4 times or more faster than silver nitrate or silver sulfadiazine[1] and it has been shown to be effective against over 150 bacterial strains and 9 clinical isolates of multiple antibiotic resistant bacteria, including 'superbugs' such as MRSA and VRSA.[2] It is also effective against 6 clinical fungal isolates including *candidas albicans*.[2] Currently, burns and chronic wounds comprise the majority of indications treated.

For use in medical devices for the treatment of wounds, that is, dressings, nanocrystalline silver coatings can be deposited on a variety of web materials, depending on the primary aspect of the wound to be treated. Different dressing types are shown in Fig. 1. For general wounds a polyethylene mesh is coated on one side then laminated with an uncoated, slightly absorbent filler, using 2 or 3 layers of coated polyethylene, depending on the duration of silver release required. The polyethylene mesh has a relatively low melting point (*c.a.* 110ºC) and a low heat capacity due to its low basis weight. For close control of moisture levels in the wound, a perforated polyurethane film is coated and used laminated to an uncoated foam backing. The polyurethane web which is coated is very thin and mechanically rather weak when unsupported. Wounds which are heavily exudating liquid, such as blood or plasma, require a highly absorbent dressing material. Calcium alginate, derived from a seaweed extract, has long been used for this purpose. A non-woven, felt-like web of this material can be coated on both sides with nanocrystalline silver, though the heavy, fibrous nature of this material and its low strength and high moisture content, present a number of challenges. This dressing is also useful for packing cavity wounds. A polyester mesh web is coated to give a conformable dressing which is particularly useful on articulations, where it improves patient comfort, and awkwardly shaped areas such as hands, making them easier to dress. However, this web material is very stretchy and can be difficult to wind evenly and flat without wrinkling.

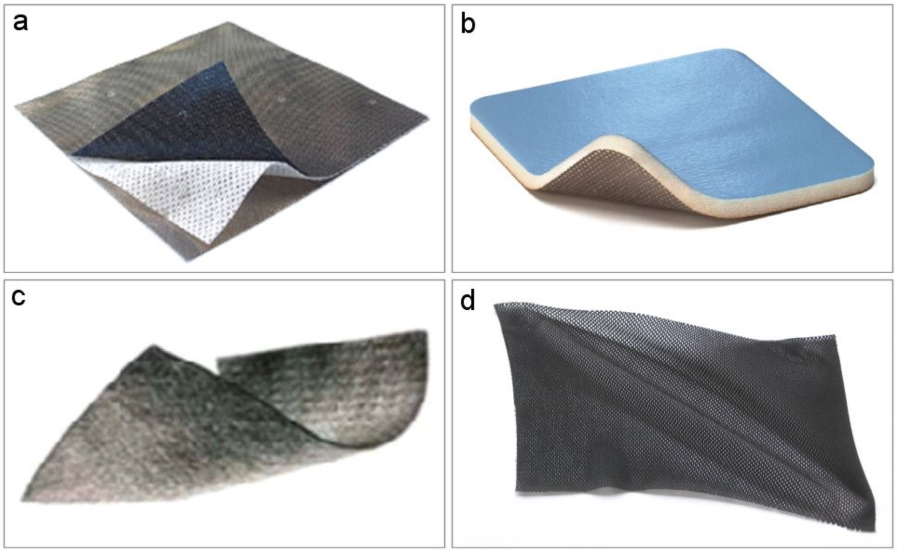

Figure 1. Antimicrobial dressings produced from nanocrystalline silver coated web materials: **a.** general dressing from polyethylene mesh; **b.** moisture control from perforated polyurethane; **c.** absorbent from calcium alginate; **d.** conformable from polyester mesh.

Staying Competitive in the Antimicrobial Silver Market: Process Optimization

In the early 1990's the dominant silver treatments were still silver nitrate and silver sulfadiazine. In 1997 sputtered nanocrystalline silver dressings were released into the market, gaining acceptance in 100 major burn centers in the USA. Expansion into the treatment of chronic wounds and other indications followed. However, there are now over 30 companies competing with antimicrobial silver formulations, while in 1995 there were none visible. In order to stay competitive in such a market, product price, and therefore manufacturing costs, must be kept down. One part of this effort is to increase the cost efficiency of sputter coating by optimization of the coating process.

Optimizing a process only makes sense within the context of what the process is actually trying to achieve and what the limitations are. The nanocrystalline silver coating is fairly thick (hundreds of nanometres) in order to provide sufficient silver in the dressing. Therefore the deposition rate has to be fairly high in order to give the desired coating thickness within a reasonable coating time. Additionally, the nanocrystalline coatings can undergo re-crystallization at relatively low temperatures, necessitating control of the total heat flux to the substrate during the process. As discussed previously, some substrates have low softening points and low heat capacity, further indicating the need to avoid excessive heat flux. Furthermore, many substrates are perforated or in mesh form and sputter-through can occur. If drum-coating is used, material can build up on the drum, possibly reducing thermal contact and limiting the effectiveness of web cooling. If freespan coating is used to avoid the problem of coating build-up on a drum, then substrate cooling is inherently poor anyway. Therefore, optimization is required to find a combination of coating process parameters which give high deposition rate but low heat flux.

Since heat flux is a major issue in this process, there is considerable advantage in being able to measure it directly. Unfortunately, no sensors appropriate for measuring heat flux in a sputtering environment appear to be commercially available. However, heat flux sensors based on thermopiles, often used in applications such as measurement of building insulation, are readily available, but need to be provided with a heat sink and protection from the sputtered material in order to be used in a vacuum sputtering process. The sensor arrangement shown in Fig. 2 was devised and found to be able to measure heat flux in a sputtering system with considerable success.

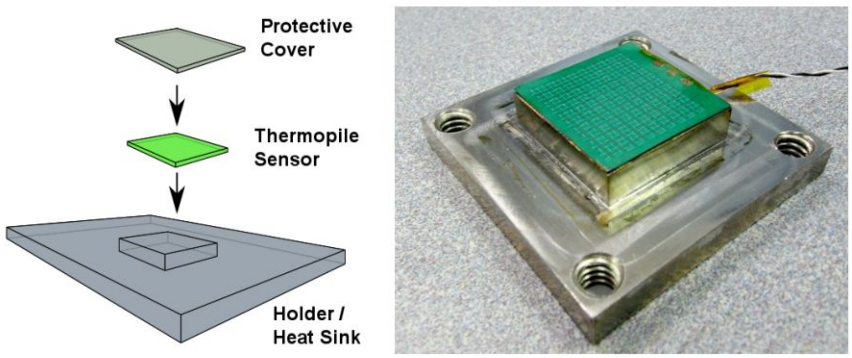

Figure 2. Heat flux sensor. The drawing on the left shows an exploded diagram of the components. The image on the right shows the assembled sensor without the protective cover.

The principal variables in the coating process are cathode current, process pressure and throw distance (the distance between the target and the substrate). Higher cathode currents, lower operating pressures, and shorter throw distances will generally all lead to higher deposition rates but also higher heat fluxes. The magnetic field of the magnetron, characterized by both its overall strength and its ‘shape’, can have a significant effect as well, adding to the complexity of the complete problem.

A typical approach to optimization might be to vary each parameter, one at a time, over some range, while measuring the changes in responses, in this case deposition rate and heat flux. An alternative is to use a design of experiments (DOE) approach, in particular factorial experiments. While there are many different possible designs of factorial experiments available, a common scheme it described here. Just two different levels are used for each parameter and experiments are performed on all possible combinations (for n parameters this gives 2^n experiments but, particularly for higher values of n, some fraction of this total number may be used). Optionally, additional experiments may be carried out at the centre point, where all parameters are at their average level (this allows an assessment of the linearity of the response).

There are a number of advantages to the factorial approach over the 'one-parameter-at-a-time' method. The total number of experiments required to give the same amount of information is reduced, since every experiment gives some information about the effect of all parameters. This also leads to better averaging of random variations in the experimental results. Additionally, parameter interactions, that is the effect of varying two or more parameters simultaneously, can be determined. However, there are a number of potential disadvantages or limitations of factorial experiments which it is important to understand. The results are only valid over the limited parameter range between the two levels chosen. However, in many optimization scenarios such a limited range is adequate. Also, the analysis of the data assumes a linear response model, which may or may not be a good approximation to the true response. Use of centre point data can indicate if there is significant non-linearity and there are techniques available to determine this quantitatively by adding further experimental data to the original set. Factorial experiments only work well with smoothly varying responses and have limited applicability to categorized parameters (e.g. pass-fail).

The use of a factorial experiment to optimize the nanocrystalline silver sputtering process will be illustrated using a representative 2-D example where only the process gas pressure and sputtering current are varied. This situation is shown in a generalized way in Fig. 3. As noted previously, increasing current and decreasing pressure will give increasing deposition rate and higher heat flux. A contour line on the diagram shows the locus where deposition rate will have some constant value. The question know is: is heat flux also constant along this contour, or does it vary, allowing heat flux to be reduced while maintaining the deposition rate? It is important to realise that this example shows only a very simple version of the full optimization problem. If other variables such as throw distance and magnetic field are added, the dimensionality of the problem increases. Furthermore, if reactive sputtering is used, chemical reactions will add further complexity.

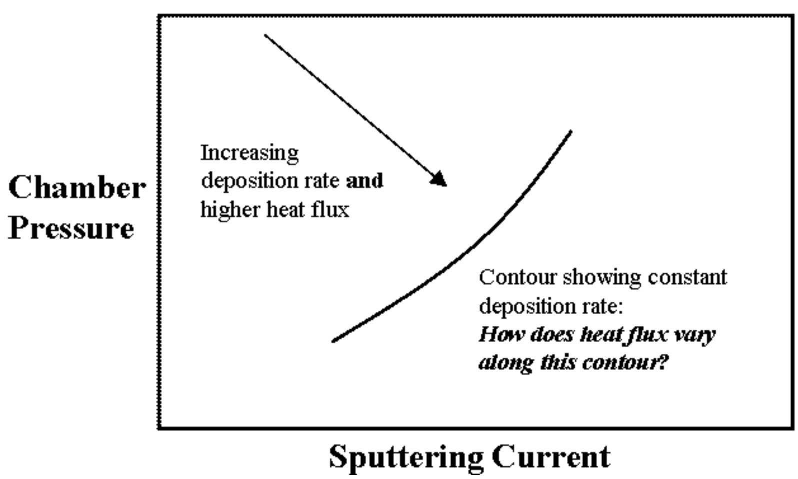

Figure 3. Illustration of the relevant aspects of the representative 2-D model under discussion.

A simple factorial experiment can be used to answer the question posed above. Pressure and current settings at two different levels, one above, the other below some centre point level (not included in this design) are used. The actual parameter values used are not important here, so these have just been coded as +1 and -1. The deposition rate and heat flux were measured at each combination of these settings (4 combinations in total). Again, the absolute response values are not important in this illustration, just the relative levels. This experiment, and the raw data obtained, are represented in Fig. 4. It can be seen, as expected, that increasing current and decreasing pressure both cause an increase in deposition rate and heat flux. The raw data can be analyzed to give model equations for the variation in deposition rate with current and pressure and these can be used to construct a contour plot of deposition rate. Such a plot is shown in Fig. 5. A similar analysis can be performed using the heat flux data, also giving a contour plot, which is superimposed on the deposition rate plot in Fig. 5. Now it can be seen that it is indeed possible to reduce heat flux while maintaining a given deposition rate, and the analysis shows a quantitative estimate of how to vary current and pressure to achieve this.

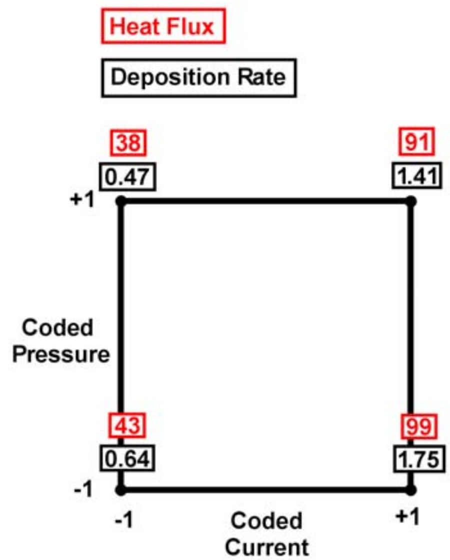

Figure 4. Factorial experiment design and measure values of responses.

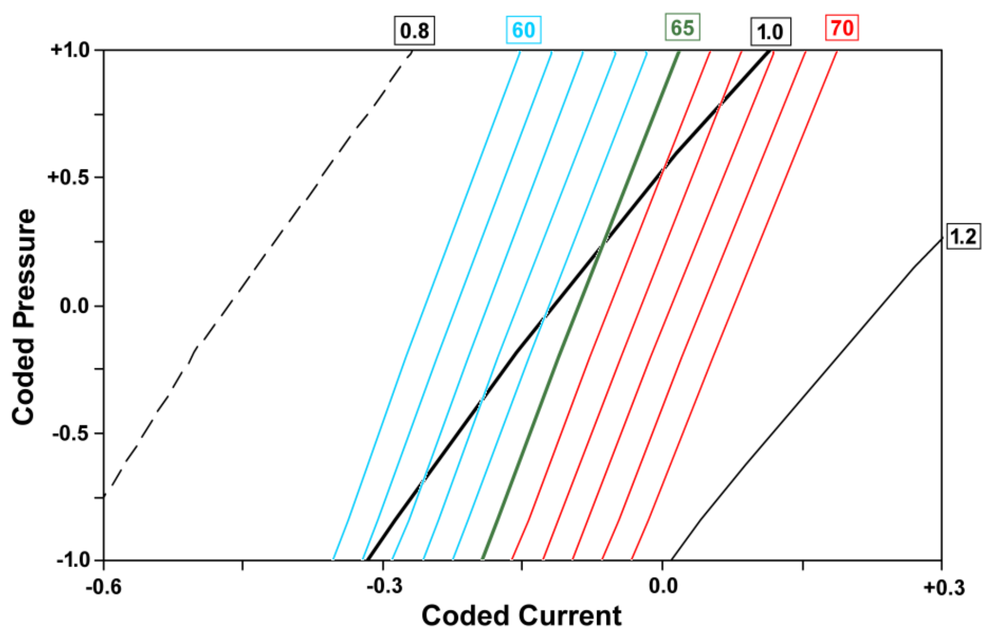

Figure 5. Contour plot from analysis of the results from the factorial experiment. Black contour lines show constant deposition rate. Coloured contour lines show constant heat flux: blue contours show heat flux lower than that of the green contour, while red contours show higher heat flux.

Future Outlook of Business and Opportunities for Growth

(or: How to survive in tough financial times)

As mentioned previously, the antimicrobial-silver wound care market is much more competitive now than it was when sputtered nanocrystalline silver coatings were first introduced. This, combined with the current financial crisis, has the potential to jeopardize the position of sputtering as a commercially viable technique for the production of antimicrobial silver. However, work on characterization, understanding and optimization of the process has helped to reduce production costs, improving profit margins and survivability and, importantly, continues to do so. Some results from this work have already been published and more will be published in the near future.[3,4] Additionally, use of efficient research, development and optimization techniques, such as DOE, helps to keep research costs down while still offering further production cost reductions and continued product development.

Therefore, sputtering remains a robust and unique process for producing products in the medical device area and there still exist many opportunities for novel films. Significant opportunities remain to grow high performance antimicrobial coatings, both on new types of web materials for treatment of different wound aspects and on other medical devices, such as various implants. Furthermore, sputtered nanocrystalline silver can be converted to a powder for incorporation into creams, gels, and other preparations. Additionally, nanocrystalline silver-based coatings have been shown to have anti-inflammatory properties,[5] which can be helpful in the healing of wounds and treatment of other conditions. Finally, outside the area of antimicrobial silver-based films, sputtering can also be used to deposit nano-structured coatings with other properties of bio-medical interest such as wear resistance on, for example, artificial joints.

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