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Research Article

A POLYMER COATED WITH ZINC OXIDE DRUG: A POTENTIAL SOLUTION FOR INFECTION-RESISTANT MEDICAL DEVICES

Dr. Rudra Gaitham Naresh*, Dr. Reddi Naresh, Dr. Yugandhar Reddy

Assistant Professor, Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry - 605 502, India

ABSTRACT

The emergence of antibiotic resistance indicates the importance of creating infection-resistant materials. In this study, the nitric oxide (NO)-releasing polymer is coated with zinc oxide nanoparticles (ZnO-NP) to boost NO release and match the endogenous NO flux (0.55 - 4010 mol cm2 min1). The ZnO-NP is utilized as a catalyst and has the added benefit of acting as an antibacterial agent when combined with NO. The ZnO-NP topcoat is applied to a CarboSil polycarbonate-based polyurethane that contains S-nitroso-N-acetylpenicillamine, a blended NO donor (SNAP). This sample, SNAP-ZnO, kept NO release over 0.5 1010 mol cm2 min1 for 14 days, but samples containing simply SNAP fell below physiological levels after 24 hours. The ZnO-NP topcoat boosted NO release and reduced the amount of SNAP leached by 55% over the course of seven days. The catalyst's lifespan within the material was determined by ICP-MS analyses, which demonstrated very little Zn ion release into the environment. In contrast to samples that did not contain NO-release, the SNAP-ZnO films had a 99.03 percent killing efficiency against Staphylococcus aureus and an 87.62 percent killing efficiency against Pseudomonas aeruginosa. Cell viability did not differ significantly between controls and SNAP-ZnO material in a cytotoxicity study performed on mouse fibroblast 3T3 cells, suggesting there was no harm to mammalian cells. A metal ion catalyst used in conjunction with a NO-releasing polymer proved to be highly effective for enhancing NO-release kinetics and antibacterial activity for device coatings.

Keywords:- Medical Device Coating, Nanoparticles of Zinc Oxide, Antimicrobial, Nitric Oxide.

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INTRODUCTION

Healthcare-associated infections (HAIs) have resulted in a host of issues [1-5], including higher healthcare costs, medical device failure, and unnecessarily deteriorating patient health.

According to the Centers for Disease Control and Prevention [6], HAIs are becoming more linked to mortality and morbidity, with one out of every 25 hospitalized patients being affected [7,8]. Medical equipment has been thoroughly researched for anti-fouling and antimicrobial materials that prevent infection [9]. Although both active and passive agents are utilized in some of the most effective treatments, active agents are the most often studied because they have a higher success rate in preventing infections over time [10], whereas Fouling can develop over time on passive surfaces. The short half-life of NO in physiological conditions explains why it is transported in the form of endogenous S-nitrosothiols (RSNOs, such as Snitrosoglutathione (GSNO) [11-16], Snitrosoalbumin, and Snitrosocysteine) [17]. In the last twenty years, however, NO has been investigated as an antimicrobial coating on medical devices and as a wound healing agent from endogenous and synthetic sources.

Corresponding Author**: Dr. Rudra Gaitham Naresh**

While N-diazeniumdiolates and other NO donors have been extensively investigated, they have limitations including limited release of NO, cytotoxicity towards mammalian cells, and unapproved by-products [18]. SNAP's shelf life is longer and it can be used as a NO donor in polymers than GSNO. It is a synthetic RSNO [19].

A range of concentrations of zinc oxide nanoparticles (ZnO-NPs) inhibited growth and caused dramatic death of Escherichia coli (E. coli) and Staphylococcus aureus when added to these bacteria [20]. The viability of primary human T cells was unaffected by the same doses. [21] By oxidizing thiol groups in essential glycolytic enzymes, Zn ions, which have a significant affinity for sulfur, stymie glycolysis in bacteria. Metal ion nanoparticles like ZnO-NPs are a good example of metal ion nanoparticles that require low concentrations for enhanced antibacterial activity and have little toxicity to human cells. [22]

The hybrid material developed in this study will have two functions: 1) to give a synergistic impact of antibacterial characteristics by combining distinct processes of bactericidal qualities displayed ZnO-NPs are catalyzed by NO and NO, and NO is released when a ZnO-NP topcoat is present.

The catalytic effects of zinc oxide nanoparticles, a much more mammalian cell friendly metal, have yet to be examined for their enhanced biological effects. Researchers previously explored the effects of Zn2+ on its ability to produce NO from and it improved NO release [23,24]. Although no studies have been conducted on the biological effects of ZnO-NPs on NO-releasing polymers, they may exhibit increased antibacterial activity or reduced cytotoxic effects [25].

For the manufacture of the material, DSM Biomedical used CarboSil, which is a thermoplastic silicone-polycarbonate-urethane. It can be treated in a number of ways and is thrombostable, biocompatible, and biostable [26]. In order to boost the durability of potential medicinal coatings, ZnO-NPs were coated on a NO-releasing polymer. In order to test SNAP's leaching capability, different amounts of ZnO-NPs were sprayed onto a topcoat with NO-releasing polymer.

In antibacterial and cytotoxicity tests, the hybrid sample is tested for its synergistic properties with NO and ZnO-NP after determining the lowest leaching (highest SNAP storage) combination [27]. There has been a study that demonstrated an increase in NO release lasting for up to 14 days and antibacterial effects lasting for 24 hours. In addition to demonstrating antibacterial activity, cytotoxic tests are performed to ensure that the finished product is safe for mammalian cells.

Procedures and Materials
Materials

To help the SNAP crystals form, the solution was stirred for 30 minutes before being placed in an ice bath. Light was prevented from the entire technique and the crystals that were created throughout the experiment.

Fabrication of ZnO-NP loaded-NO Releasing Films

Thirty-one billion parts per million (ppm) of CarboSil were dissolved in THF for SNAP films. DSM sells CarbonSil, a polyurethane based on polycarbonate and silicone. Using this compound in conjunction with SNAP has proven to achieve stable NO-releasing characteristics, which has been used by our group and others. The company's website includes details about the specific properties of CarboSil 30–32. After the CarboSil was dissolved completely, 10% SNAP was added. A TeflonTM mold was then poured with the solution, which was then left to cure overnight in the dark. Circular disks of 8 mm diameter were cut from the dried films. Each sample was separated into batches containing 0, 1, 5, and 10% ZnO-NP after making 25 mg ml1 of CarboSil solutions. The circular films were dipped in the prepared solution, and the films were dried for 10 minutes between coats, before being top coated twice with the ZnO-NP solution. Sigma-Aldrich provided ZnO-NP for this experiment. The purity of the ZnO-NP was stated as >97% and its size was described as 50nm. All films were allowed to dry completely for 24 hours before being used in tests.

SNAP Leaching Analysis

SNAP leaching was monitored via UV-Vis spectrophotometry on the produced circular films. At various time intervals over the course of 7 days, To determine the amount of SNAP leached into the PBS (which was used to soak the film), the wavelength of 340 nm (maximum absorption of the S-nitroso bond in SNAP) was measured. To determine the initial level of SNAP, samples were weighed before the topcoat was applied. We soaked the emulsions in PBS with EDTA at 37°C after they had been coated with the top coat. Calibration curves were used to compare the measurements.

Nitric Oxide Release Measurements

Utilizing a Siever's Nitric Oxide Analyzer (NOA) (Boulder, CO), we analyzed the SNAP-ZnO films compared with SNAP films in terms of chemiluminescence. With and without ZnO coatings, NO release from SNAP-containing films was measured. A reaction cell containing PBS buffer containing amber reaction samples was placed at 37°C. A chelating agent, EDTA, was added to the PBS buffer in order to prevent a catalytic release of NO by free metal ions. Nitrogen gas was used to remove NO from the solution. In PPB, purged NO was delivered using sweep gas to the detecting chamber.

Inductively Coupled Plasma Mass Spectroscopy (ICP-MS)

A VG ICP-MS Plasma Quad 3 apparatus was used to determine the metal-ion nanoparticle content (ZnO, in this case) in the leachate samples. DMEM was immersed in samples with ZnO topcoats for two weeks at 37 degrees C to study the effect of the topcoats on DMEM. A test of the isotopic composition of the films was conducted after the two weeks had passed.

Bacterial Adhesion Research

The bacterial adhesion to the produced materials was tested using an ASTM E2180 technique that had previously been established.

This protocol was followed with only minor modifications. Researchers used carboSil, ZnO, SNAP, and SNAP-ZnO in the bacterial adhesion experiment. The antibiotic efficacy tests were conducted using Staphylococcus aureus and P. aeruginosa. A mid-log phase of 106-108 CFU ml1 was achieved in LB broth at 37°C using the cultuIncubation of samples was then performed with resuspended bacteria in PBS.ples. Each sample was incubated in a shaker incubator (37°C, 200 rpm) for 24 hours with 2 mL of bacterial solution. Incubation of bacteria was followed by 24 hours of rinsing with DI water to eliminate any unattached bacteria. All samples were homogenized for one minute each prior to being put in buffer solutions to remove any adhering bacteria. The buffer solutions were serially diluted (up to 105) before being plated on LB agar and incubated at 37°C in the incubator. In this manner, bacteria from the materials were now present in the buffer solutions prior to plating on LB agar. After incubation for 18 hours, the colonies of bacteria were counted. We normalized the number of CFUs with respect to the area exposed to bacteria in each sample by using the following formula:

Cytotoxicity investigations

The cytotoxicity of murine fibroblast cells was investigated using a previously approved and published cell cytotoxicity assay (3T3).

25 Culture of mouse fibroblasts was performed in an agar plate containing Dulbecco's Modified Eagle's Media (DMEM) containing 5% glucose, 10% Fetal Bovine Serum, and 1% antibiotics (Penn-Strep). After cell confluency reached 80–90%, the medium was replenished every other day.

A second 24 hours of incubation in the incubator followed the introduction of leachates into the well-containing cells after the 24 hours had passed. In a subsequent step, 10 l of WST-8 solution was added (CCK-8 kit, Sigma Aldrich), and the mixture was incubated for 4 hours as directed. Using a photoplate reader, formazan at 430 nm could be measured only by live fibroblast cells, as they produced NADH that converted WST-8 to formazan. In respect to CarboSil, the relative vitality of the cells was estimated using the formula below (cells exposed to CarboSil leachates).

The percentage of cell viability is equal to the absorbance of the test samples. CarboSil samples have a 100 percent absorbance.

Statistical Analysis

All of the data is described using the mean and standard deviation. In the technique section, the number of replicates for each experiment is indicated.

Results

Surface Characterization, NO Release Kinetics, and Film Fabrication

The test was conducted on films containing varied amounts of ZnO-NPs on films with consistent SNAP content, as indicated in Table 1. ZnO-NP was measured in weight percent to determine how much was needed for an optimal SNAP storage and long-term NO release. The amount of SNAP required to release NO continuously has previously been determined as 10% by weight. We investigated the impact of ZnO-NP topcoated films on SNAP preservation after seven days in PBS (pH 7.4, 37°C). High SNAP retention in the polymer is critical for assuring long-term NO release from the drug while avoiding any cytotoxic consequences. After 7 days, the SNAP-ZnO films had the least amount of SNAP leached, with only 7.75 0.51 wt.%, whereas films containing solely SNAP had the most (13.86 3.62 wt. percent).

In the polymer matrix of CarboSil, SNAP crystals form because the polymer uptake is low. The molecule crystallizes when its solubility exceeds the SNAP solubility threshold, stabilizing the NO donor and increasing the duration of NO release. 34,35 According to previous research, all films were made with 10% SNAP to get the best SNAP crystallization while maintaining the polymer's mechanical properties. 35 The NO flux for the SNAP-ZnO films remained within the physiological range of 0.5 to 4.0 (x1010 mol min1 cm2) released by the endothelium for approximately 14 days (Figure 3, Table 3). While the NO flux in the SNAP samples initially spiked at 3.57 0.814 (x1010 mol min1 cm2) (Day 0 not shown in figure), it quickly dropped to 0.24 0.045 (x1010 mol min1 cm2) within 24 hours and was below 0.10 (x1010 mol min1 cm2) by day 14.which was just below physiological values, ongoing study has shown that these levels are still antibacterial. 36

Using EDS, zinc and sulfur were determined in the mapped films (SNAP-ZnO) and analyzed to confirm that the samples' surfaces were evenly coated with ZnO-NPs. The uniform blending of SNAP and ZnO-NPs revealed that the production method had no negative impact on SNAP or ZnO-NP stability.

The leaching of ZnO-NP was studied

In order to facilitate NO-release from the blended SNAP, a large portion of ZnO-NP must remain within the tested polymer films. ZnO-NP has a variety of advantages and is required by a number of physiological pathways. The 1 cm2 measured samples were subjected to ICP-MS in order to determine whether ZnO-NP diffusion was occurring. ICP-MS analyses of all ZnO-NP samples were conducted using only the highest weight percentage (10%) of ZnO-NPs to discover any potential environmental contamination. When ZnO films were soaked in DMEM at 37°C for 14 days, the total Zn leached into solution was only 1.08 percent, whereas SNAP-ZnO films were 3.17 percent.

Antimicrobial Efficacy and Cytotoxicity of NO-Releasing Materials Topcoated with ZnO-NP

NO's antibacterial properties make it possible to reduce the risk of biomedical device infections and HAIs through its active release from donor molecules in hydrophobic polymeric films. Further bactericidal effects of metal ions may be used in conjunction with an increased NO release to diminish bacterial adhesion to NO-releasing materials. On CarboSil samples, solely ZnO-NPs topcoat is used, S. aureus counts are decreased by 78.02 25.03 percent (0.5 log). As mentioned in the introduction, ZnO-NPs possess bactericidal properties. NO-releasing CarboSil (SNAP films) had significantly greater bactericidal power than diffusion based NO cytotoxicity due to significantly stronger NO bactericidal powers (one log). However, with a 99.03 0.50 percent reduction (2 log) of SNAP-ZnO films, these synergistic benefits are evident. As a topcoat, ZnO-NPs exhibit greater bactericidal activity against S. aureus when applied with SNAP-containing polymers, suggesting synergistic effects of ZnO-NPs and NO. The ZnO/SNAP-ZnO ratios were also reduced substantially (95.59 2,29%), as well as the SNAP/SNAP-ZnO ratios (92.11 4,10%).

This could be because Gram negative bacteria, such as P. aeruginosa, have an extra cell membrane. ZnO was reduced by 60.98 14.18 percent (0.5 log) when compared to CarboSil, and SNAP materials were reduced by 63.76 14.88 percent. A comparison of SNAP-ZnO materials and CarboSil samples showed an 87.63 percent reduction (one log) when combined with both bactericidal agents. At a p value of 0.05, these reductions were all statistically significant. ZnO-NPs and NO's antibacterial action are believed to combine to produce this higher reduction. There was also a considerable reduction of 65.86 13.42% between ZnO and SNAP-ZnO, and 68.29 12.46% between SNAP and SNAP-ZnO. Researchers have evaluated ZnO nanoparticles in combinations with NO donors to determine whether the hybrid materials have improved infection-resistant properties and might be suitable for use on medical devices (Table 4).

When evaluated on mouse fibroblast cells, this means the chemical has no cytotoxicity. This minimal cytotoxicity was expected based on the It also serves as proof-of-concept for the material's possible biocompatibility since it contains Zn ions (ICP-MS data) and SNAP analysis results.

Table 1: Every sample has its own composition.

Sample Fabrication		
Example	**BASIS FILM**	**OVERLAY**
CARBOSILIC	CARBOSIL 50 mg/ml	Dip in CarboSil 25 mg/ml solution twice
ZincO-1	solution 50 mg/ml	2 dips of 25 mg/ml CarboSil solution containing 1 wt.% ZnO-NP
powder	in CarboSil at 50 mg/ml	25mg/ml of carboSil with 15 wt.% ZnO-NP dipped twice
solution	in CarboSil at 50 mg/ml	A 25 mg/ml CarboSil solution containing 5% ZnO-NP was dipped two times.
SNAP	CarboSil 50 mg/ml with 10% SNAP	solution diluted in 25 mg/ml CarboSil
SnN-1	CarboSil with 10% SNAP, 50 mg/ml	A CarboSil solution containing 1 weight percent ZnO-NP at 25 mg/ml was applied twice
5-SNAP-ZnO	10 wt.% SNAP in CarboSil 50 mg/ml	Dips in CarboSil solution containing 5 weight percent ZnO-NP containing 25 mg/ml
ZnO-SNAP	CarboSil 50 mg/ml with 10 wt.% SNAP	2 dips of 25 mg/ml CarboSil® solution containing 10 wt% ZnO-NP

Table 2: The following table provides additional information on the SNAP withdrawal rates.

Wt. Leached	%			of			SNAP
	1 hour	**4 hours**	**24 hours**	**48 hours**	**72 hours**	**96 hours**	**168 hours**
Snack	1.71 ±1.54	3.74 ±1.93	5.33 ±2.10	7.80 ±1.97	9.80 ±1.97	11.52±2.50	13.85 ±2.95
NACZ-1	0.44 ±0.41	2.07 ±0.51	3.93 ±0.58	6.21 ±0.82	8.11 ±0.95	10.88 ±2.36	12.71 ±2.60
SNAP-ZnO-five	0.01 ±0.01	1.07 ±0.31	2.36 ±0.40	4.38 ±0.50	5.38 ±0.25	6.85 ±0.33	8.81 ±0.25
SnO2	0.20 ±0.31	1.37 ±0.33	2.51 ±0.31	4.46 ±0.65	4.98 ±0.38	6.07 ±0.41	7.74 ±0.40

(Note: Because the SNAP crystals are permitted to dissolve and blend with the polymer/THF solution before being casted into the molds, SNAP loading efficiency in all SNAP-based films is expected to be 100%.)

Table 3: SNAP films vs. SNAP-ZnO films for 14 days: NO release (x10*10 mol cm*2 min*1) compared to SNAP films.

	Day 1	**Day 3**	**Day 5**	**Day 7**	**Day 11**	**Day 14**
Snapping	0.240 ±0.044	0.221 ±0.022	0.234 ±0.083	0.202 ±0.047	0.122 ±0.060	0.078 ±0.042
SNAPO	2.765 ±0.426	1.751 ±0.144	1.252 ±0.128	0.850 ±0.018	0.648 ±0.027	0.486 ±0.074

Table 4.: The test samples were less contaminated with bacteria/cm2 than those treated with CarboSil.

	Reduction in *Staphylococcus aureus* (%)	**P. aeruginosa reduction (%)**
CarbonSil vs. ZincO	78.01 ±25.02	60.97 ±14.17
Comparison of CarboSil and SNAP	87.71 ±7.52	63.75 ±14.88
SNAP-ZnO vs. carboSil	99.02 ±0.51	87.62 ±4.85
ZnO versus SNAP-ZnO	95.58 ±2.28	65.85 ±13.41
SAP vs. SAP-ZnO	92.10 ±4.11	68.28 ±12.45

Discussion

Because of their poor leaching qualities, SNAP-ZnO samples are expected to produce NO for a long time. The increased SNAP-ZnO films showed greater durability for long-term indwelling applications, as expected, which will reduce infective complications. Because the SNAP-ZnO samples consistently enhanced NO release, they were ideal for determining antibacterial efficiency and cytocompatibility.

SNAP and metal ion element distribution were tested after NO storage and release characterization [5,14]. The homogeneous distribution of the coating makes it likely that it will prevent microbial adhesion to the surface of the medical device.

A transition metal ion can accelerate the breakup of sulfur-nitrous bonds in all RSNOs into radical NO and disulfides. Utilizing RSNOs, we have thoroughly investigated the catalytic properties of Cu2+ metal ions being reduced to Cu+ [8]. Zn has been shown in the past to exert a similar catalytic effect, although the specific process is still being investigated. Since Zn2+ retains its ionic state through the entire catalytic process [10], it is more specific than Cu+ for the Zn2+-mediated reactivity of RSNOs. An aqueous environment forms disulfide RSSR compounds as RSNO degrades to RS- + NO. Using RSH molecules in Zn integrated SNAP films would be advantageous in promoting NO release.

In the case of SNAP-ZnO samples, a very small amount of Zn ions were leached (3.17 percent), which indicates that the nanoparticles had been adequately retained possibly increasing Zn solubility and resulting in a somewhat higher leachate result. The SNAP-ZnO films could be more effective at inhibiting bacteria through increasing Zn leaching.

Medical implants are prone to bacterial adhesion. An inflammatory response is triggered when medical devices come into contact with the fluidic biological environment provided by human physiology, including surgical wounds created during implant procedures. This bacterial adhesion can result in site infection, medical device failure, and even mortality in the initial few hours following implantation. Two of the most common nosocomial infections are Staph aureus and Pseudomonas aeruginosa. For the reasons stated, S. aureus and P. aeruginosa were used in a 24-hour bacterial adhesion study on the fabricated materials. It's also worth noting that both bacteria studies took place after the items had been soaked in PBS for 24 hours. Through this

process, metal-ion leachates and SNAP leachates from the original study were removed, to prevent any false results caused by a high concentration of leachates during bacterial incubation. It was observed that SNAP-ZnO samples decreased bacterial adhesion more than any other sample studied for both species. The combination of antibacterial action of ZnO-NPs and NO, as well as improved NO release, resulted in increased antimicrobial activity. Despite the fact that NO and ZnO-NPs exhibit antibacterial characteristics on their own, the results reveal that they work additively when combined in the SNAP-ZnO composite.

Despite its controlled No release and antimicrobial activity, the chemical must also be free from harmful effects on mammals. During the application process, protecting the host tissue from harmful side effects would be important.

Copper nanoparticles have also been shown to enhance NO release from SNAP,41 despite the same dose of SNAP being shown to have little cytotoxicity. SNAP and ZnO together yielded comparable results for the first time, however. NO-based approaches also have the advantage that they are compatible with a wide array of bacteriostatics and bactericides. 31,42–44 It could be utilized as an alternative to silver nanoparticles or antibiotics, which can produce cytotoxicity or bacterial resistance, due to its non-cytotoxic nature and antibacterial characteristics.

Conclusion

In this study, early test data has been compiled to develop a long-lasting biocompatible and antibacterial device applicable to a variety of implantable materials applications. Eventually, it is planned to develop and test in vivo metal-ions that can be combined with NO donors to initiate nitric oxide release in mammalian cells.

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