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A Surface Coating that Rapidly Inactivates SARS-CoV-2

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ABSTRACT

SARS-CoV-2, the virus that causes the disease COVID-19, remains viable on solids for periods of up to one week, so one potential route for human infection is via exposure to an infectious dose from a solid. We have fabricated and tested a coating that is designed to reduce the

longevity of SARS-CoV-2 on solids. The coating consists of cuprous oxide (Cu_2O) particles bound with polyurethane. After one hour on coated glass or stainless steel, the viral titer was reduced by about 99.9% on average compared to the uncoated sample. An advantage of a polyurethane-based coating is that polyurethane is already used to coat a large number of everyday objects. Our coating adheres well to glass and stainless steel, as well as everyday items that people may fear to touch during a pandemic, such as a doorknob, a pen, and a credit card keypad button. The coating performs well in the cross-hatch durability test and remains intact and active after 13 days immersed in water, or after exposure to multiple cycles of exposure to virus and disinfection.

1. INTRODUCTION

COVID-19 has caused widespread human morbidity and mortality, as well as disruption to our economy and our way of life. The disease is spread through the virus, SARS-CoV-2, which is known to remain viable on some solids for periods of up to one week.[1-2] One potential route of human infection occurs when a person comes into contact with a solid that is contaminated with the virus (a fomite), so one method of reducing transmission would be to reduce the period of human vulnerability to infection by reducing the period of viability of SARS-CoV-2 on solids. In this report, we describe the fabrication and testing of an anti-SARS-CoV-2 coating. Our ultimate goal is to produce a coating that (1) inactivates the virus quickly, (2) can be coated on many solids, and (3) is sufficiently robust that it retains virucidal potency during consumer use. Such a film could be used on many household, commercial, medical, and manufacturing surfaces, such as doorknobs, credit card buttons, and cell phone covers. These are objects that a person might touch only minutes after deposition of respiratory droplets. Our hope is that widespread use of such a coating could reduce transmission of SARS-CoV-2 and also reduce fear of touching objects.

At our starting point, it was unknown which chemical groups inactivated SARS-CoV-2. We tested three films. Two of the films were monolayers of cationic polymer: cationic groups are known to inactivate other viruses[3-4] (and bacteria[3-5]), and the mechanism is believed to be that the high density of charge disrupts the self-assembly of the pathogen. These films did not have a significant effect. We chose cuprous oxide (Cu_2O) as the active ingredient of the third film. Prior work demonstrated that SARS-CoV-2 had a short period of viability on Cu metal,[1] and the surface layer of Cu metal readily oxidizes to Cu_2O.[6] Cu_2O has shown activity against two other viruses: a bacteriophage by exposure to unbound particles[7] and hepatitis C by exposure of the virus to suspended nanoparticles.[8]

Cuprous oxide is used as pesticide and is rated as Toxicity Category III by the EPA which means that it is slightly toxic and slightly irritating.[9] It is also used as marine antifoulant and it known to have an adverse effect on marine organisms.[10-11] However, a review of clinical and animal studies of textiles containing copper oxide by Borkow reports no effects on human skin.[12] For copper pesticide products more generally, according to an 2009 EPA report:[9] “Current available literature and studies do not indicate any systemic toxicity associated with copper exposure. … There are no residential or occupational risks of concern resulting from exposure

to copper products." Likewise, immune response to copper is rare, whereas contact with copper in coins, intrauterine devices and other applications is common.[12]

In this work, we describe the time-course of inactivation of SARS-CoV-2 on Cu_2O particles bound into a thin (10–16 μm) film with a commercial polyurethane (PU) (Fig 1.). The commercial polyurethane is already formulated to be hard-wearing and easy to apply to many materials. Our results show that the Cu_2O/Pu coating inactivates the virus very quickly: viable viral counts drop by an average of about 99.9 % in 1 h. The film is robust and retains its potency to SARS-CoV-2 after multiple cycles of exposure to the virus followed by disinfection.

2. MATERIALS AND METHODS

2.1 Materials. Cu_2O particles (Chem Copp HP III Type UltraFine -5) were purchased from American Chemet Corporation. The chemical composition and particle size distribution information are described in Table S1 and Figure S1. Polyurethane (Miniwax, Fast-Drying Polyurethane, clear satin) was purchased from Lowes Home Improvement Store. The following chemicals were purchased from Sigma Aldrich: (3-glycidyloxypropyl)trimethoxysilane (GOPTS) (>98%), poly(diallyldimethylammonium chloride)(PDADMAC) (average M_W = 400 000-500 000,

20 wt% in water). Polyallylamine (PA) in freebase form (MW = 15 000, 15% in water) was purchased from Polysciences. The following items were obtained from VWR: glass slides (25 × 75 × 1 mm), toluene (ACS grade), ethanol 200 PROOF, nitric acid (70%, ACS grade), sodium chloride (ACS grade). Stainless steel 301 shim (thickness 0.25 mm, McMaster Carr) was cut into 13 × 13 mm pieces, washed with soap and water, and rinsed with water. Water was purified by a Barnstead EASY pure II unit.

2.2 Fabrication of the Films. The Cu_2O/PU coating was fabricated as follows. A very thin layer of PU was applied to a glass slide using a sponge and then left to dry for approximately 8 minutes to allow partial curing of the polymer. At this time, the film showed only slight or zero marking when touched with a gloved hand. 10% Cu_2O in ethanol suspension was sonicated for 3 min. and then 1 mL was applied to the PU film and left to partially dry for about 5 minutes at room temperature. The film was then heated in an oven at 120 °C for 2 hours to finish the cure, forcefully blown with compressed nitrogen gas, washed thoroughly with DI water, and dried with a stream of nitrogen gas. At this point the film had a high advancing contact angle for water, approximately 130º. The glass film was broken into ≈ 12×12 mm pieces. Each piece of glass or stainless steel was then cleaned with argon plasma to remove excess polyurethane (See Figure S2). For the plasma cleaning, the sample was placed in vacuum, twice purged in argon gas for

10 minutes, then exposed to argon plasma for 3 min at 100 W and <200 mTorr. After plasma cleaning, the film was wetted by water, but the advancing water contact angle was recovered after one day. This is the state in which SARS-CoV-2 inactivation was tested and all other tests were performed unless otherwise specified. The films showed no visible change after immersion in water for 7 weeks or ethanol for one month. When we replaced the oven treatment with 24 h of cure, the outer layer of the film was less stable but a robust layer remained on the solid (**See Supporting Information**).

The PA film was prepared as described previously.[5] Briefly, the glass was rinsed three times with DI water, soaked in 70% ethanol for 15 min, and rinsed 3 times with DI water. Subsequently, the glass was immersed in 6 M nitric acid for 20 min, then thoroughly rinsed in DI water. The glass was then exposed to oxygen plasma, treated with pure GOPTS at 37°C for 60 minutes, and then with 15% PA in water (pH = 11) and left to react at 75°C for 36 h in a closed container. Subsequently the films was rinsed with DI water (10 times) to remove unattached polymer chains, and dried with nitrogen gas.[5] For the PDADMAC surface, the cleaned glass was immersed in 1 mM PDADMAC / 10 mM NaCl for 3 h and then gently rinsed in DI water and dried with nitrogen gas.[13]

2.3 Characterization of the Cu_2O Films. An SEM image of the film in cross-section is shown in Figure 1 and a plan view is shown in Figure S2 along with images of a film before plasma treatment. As a result of fabrication from a polydisperse particle distribution, the final film has a distribution of particle sizes, and is rough; the thickness ranged from 10–16 μm. Contact angles were measured using a First Ten Angstroms FTA125. Water contact angles of the film one week after fabrication were advancing: 120 º, receding: < 10º, and sessile in the range 80–120º. The chemical composition of the film was investigated by X-ray photoelectron spectroscopy (XPS, PHI VersaProbe III with a monochromatic Al Kα source of 1486.6 eV) as well as Electron Dispersive X-ray Spectroscopy (EDX, Bruker Quantax) and Scanning Electron Microscopy (SEM, FEI Quanta 600 FE-ESEM). Results confirmed the chemical identity of the Cu_2O particles in the film, and are contained in Supporting Information, Figure S3. and Table S2. The robustness of the film was measured by the cross-hatch test ASTM D3359 Method B and peel test ASTM D1876.

2.4 Characterization of the Cationic Films. The PA and PDADMAC film contact angles were < 10º, and the chemical compositions and XPS (Figure S4 and S5) were consistent with the chemical composition.

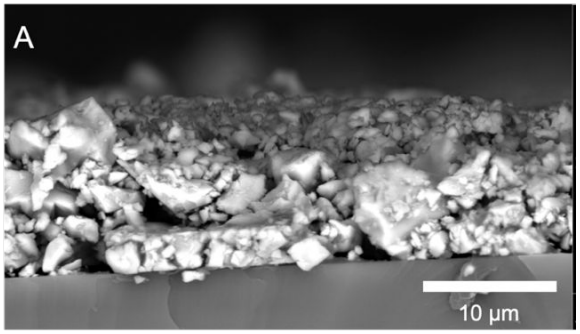


Figure 1. A. Cross section view of the Cu_2O/polyurethane film.

2.4 Inactivation of SARS-CoV-2. Biological testing methods are described in Chin et al's prior work.[2] Briefly, before testing with SARS-CoV-2, the film was disinfected with 70% ethanol in water and air dried at 37 ºC overnight, unless otherwise stated. SARS-CoV-2 was isolated from the index case of Hong Kong. Stock virus was prepared by Vero-E6 cells cultured in Dulbecco's Modified Eagle Medium supplemented with 2% fetal bovine serum and 1%v/v penicillin-streptomycin at 37°C with 5% CO_2. A 5 µL test droplet containing 6.2 x 10^7 (7.8 log unit) $TCID_{50}$/ml SARS-CoV-2 was placed on the test solid at 60–70% humidity and 22–23°C and was observed to dry in about 15 min for more hydrophilic samples and about 30 min for more hydrophobic samples. After a prescribed time, the solid was soaked in 300 µL of viral transport medium (Earle's balanced salt solution supplemented with 0.5%(w/v) bovine serum albumin and 0.1%(w/v) glucose, pH 7.4) at room temperature (≈ 22°C) to elute the virus. The

eluted virus was titrated by 50% tissue culture infective dose ($TCID_{50}$) assay in Vero E6 cells.[14-15] In brief, confluent Vero E6 cells on 96-well plates were infected with serially diluted virus in quadruplicates. The infected cells were incubated at 37°C with 5% CO_2. On day 5 post-infection, the cells were examined for a cytopathic effect. The $TCID_{50}$/ml is the dilution that caused a cytopathic effect in 50% of treated Vero E6 cell cultures (N=4 per each dilution; Reed-Muench method[16]). Three independent tests were done at each condition, except for the data in Figure S8, where there were 6 independent measurements. Error residuals were approximately normally distributed after a log transformation (Figure S6), so all averages were calculated from the log of the titers. Because reductions in titer were very large, we make use the "log reduction" terminology of biology:

$$\log \text{reduction} = \text{mean}\left[\log_{10}\left(\frac{\text{uncoated titer}}{\text{units}}\right)\right] - \text{mean}\left[\log_{10}\left(\frac{\text{coated titer}}{\text{units}}\right)\right] \quad (1)$$

$$\%\ \text{reduction} = \left[1 - 10^{-\log \text{reduction}}\right] \times 100 \quad (2)$$

For example, a 99.9 % reduction is the same as a 3-log reduction.

3. RESULTS AND DISCUSSION

3.1 The Cu_2O/PU Film Rapidly Inactivates SARS-CoV-2.

Inactivation of the virus by the Cu_2O/PU coating is swift and dramatic, typically a reduction of 99.9% of the viral titer in 1h (Figure 2). The virus is slowly inactivated even on glass or stainless steel, so in Eq. 1 we always use as our basis of comparison the titer on the uncoated sample at the same time point. Clearly, the numerical reductions would be even greater if we were to compare to the viral titer at time zero.

On glass, the SARS-CoV-2 titer was below the detection limit after 1h for all three samples, and at all further times, so the reduction is at least 99.98% (Table 1). The 95% confidence interval is the range greater than 99.5%. On stainless steel the reduction was 99.90% after one hour. The reductions in titer on glass and stainless steel are very similar because the virus interacts with the coating, not the underlying material. Films were fabricated by hand so some variation may be due to differences in sample preparation as well as in testing. Numerical values of data points are in Tables S3-10. The effects of polyurethane-only coating were not resolved (p >0.05 at 1 h), demonstrating that Cu_2O is a necessary ingredient in the film. Figure S7 shows the time course of viral titer on polyurethane.

Several Mechanisms for the biocidal activity of cuprous oxide compounds have been proposed, and the mechanism may vary according to the microbe. Fujimori reported that the mechanism was dissolution of Cu^+ followed by production of reactive oxygen species (ROS), e.g., $OH\cdot$. These ROS would then go on to degrade viral proteins.[17-18] In contrast, Sunada et al. reported that direct contact with Cu_2O with a virus was required for virucidal activity,[7] and Hang report that Cu_2O can inhibit infection by preventing virus entry.[8] The inhibitory mechanism of Cu_2O on SARS-CoV-2 is beyond the scope of this study, but further investigation on this topic is warranted.

It is interesting to note that time course of inactivation appeared to be affected by the wettability of the Cu_2O/PU film. The first batch of coating that we made produced high sessile contact angles of viral culture medium, >90º (possibly due to some polyurethane on the surface), whereas later batches had lower angles, $\approx 45^{o}$ (precise measurement not available in the BSL-3 lab.). XPS and SEM characterizations are from the later batches. When the angle was high, we were able to detect a small amount of virus at 1 h on some replicates (See Figure S8.) We rationalize this effect in terms of higher contact area between the viral suspension and the coating and/or faster transport within the liquid that were able to partially penetrate the film.

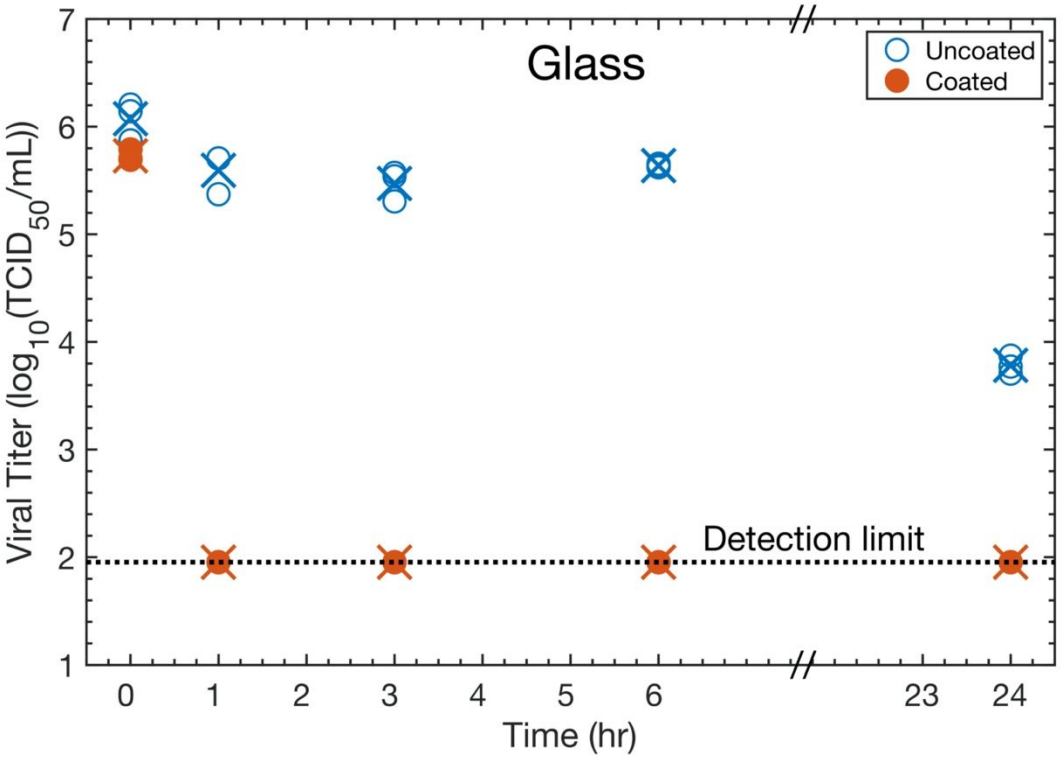
condition	comparison	% reduction	log reduction	95% CI*	*p*-value	Figure no.
Cu_2O/PU coating on glass	glass	>99.98	>3.64	99.95	5×10^{-4}	2
Cu_2O/PU coating on stainless steel	stainless steel	99.90	2.97	98.51	8×10^{-3}	2
PU coating on glass	glass	10	0.04	-164	0.22	S7
Cu_2O/PU on glass, stored 13 days underwater	glass†	99.96	3.39	99.56	8×10^{-4}	S10
Cu_2O/PU glass, high contact angle	glass	99.89	2.97	99.22	2×10^{-6}	S8
Cu_2O/PU glass, 5× disinfection	glass	99.89	2.95	99.79	4×10^{-8}	3

* 95% confidence limit lower bound. Upper bound set at 100%. Calculated for one-tail, assuming heteroscedastic.

† Comparison sample not stored under water.

p-values for Student's t-test calculated for one-tail, assuming heteroscedastic.

Table 1. Average reduction of SARS-CoV-2 titer on Cu_2O/PU coated solid in 1 h compared to titer on uncoated solid in 1h.


Glass
Uncoated
Coated
Detection limit
Viral Titer (log10(TCID50/mL))
Time (hr)
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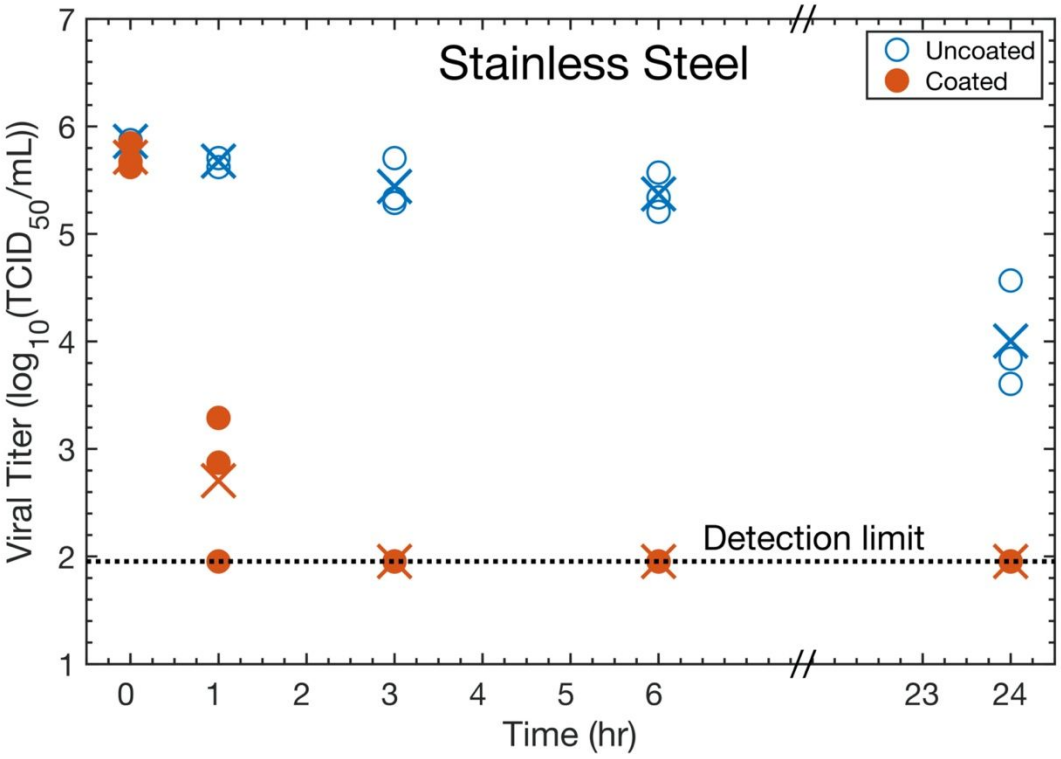
Stainless Steel
Uncoated
Coated
Detection limit
Viral Titer (log10(TCID50/mL))
Time (hr)
0
1
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5
6
23
24
1
2
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4
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6
7

Figure. 2. Time course of viable titer of SARS-CoV-2 on solids, with and without a coating of cuprous oxide microparticles bound with polyurethane (Cu_2O/PU). Note that the vertical axis in on a log10 scale. Data is shown for coated glass and coated stainless steel. Individual circular data points represent each independent measurement and the × symbol represents the mean of the log of independent measurements. The detection limit was 90 $TCID_{50}$/mL (shown with a dotted line). Experimental results where virus was not detected are plotted at 90 $TCID_{50}$/mL and are included in the average as 90 $TCID_{50}$/mL. SARS-CoV-2 is inactivated much more rapidly on the coated surface than on the bare surface.

The coating is easy to apply to everyday objects because the first stage of the coating procedure is to paint with a commercial polyurethane, which has been formulated to adhere to a variety of surfaces. The Supporting Information (Figure S9) shows images of various items – a doorknob, a credit card reader “Enter” button, a pen and a supermarket cart handle – coated in the Cu2O/PU film.

We also note that there was no cytopathic effect to the Vero-E6 cells after exposure to the viral transport medium that had been in contact with the Cu2O/PU film, consistent with low toxicity of the film.

3.2 The Cu2O/PU Film Remains Potent after Multiple Exposures to Virus or Storage under Water

To determine the potency of the film for inactivating virus after multiple exposure to virus, we applied a 5 μL droplet of SARS-CoV-2 to a Cu_2O/PU-coated surface and allowed the droplet and then its dry residue to stand for 24 h to ensure inactivation of virus. The coated solid was then cleaned by soaking in 70% ethanol. After air drying, another 5 μL virus droplet was applied on the same spot of the surface. These procedures were repeated 5 times and then we tested the ability of the coating to inactivate SARS-CoV-2 as described in the methods section. The film remained potent for inactivating SARS-CoV-2: after 5 exposure/disinfection cycles, the film still reduced the viral titer by about 99.89% in 1 h (See Figure 3), which is similar to the potency of the same films prior the disinfection cycles (99.88%)(See Figure S8).

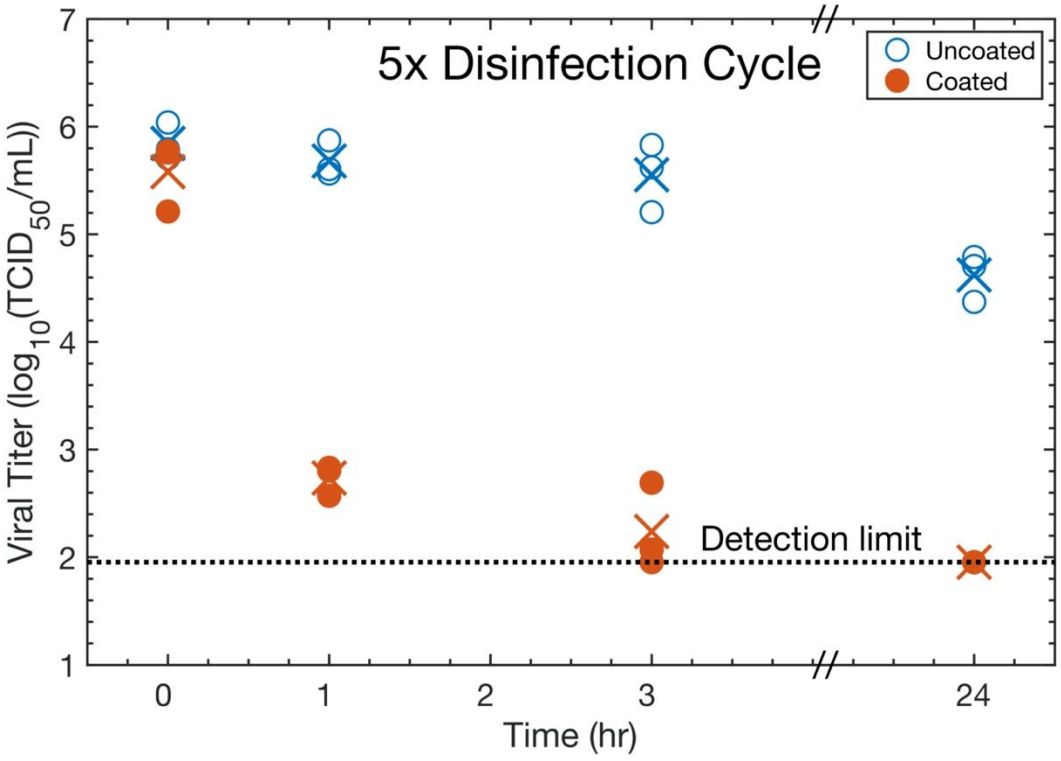

Figure. 3. Time course of viable titer of SARS-CoV-2 on glass coated in Cu_2O/PU that was subjected to 5 cycles of exposure to SARS-CoV-2 plus soaking in 70% ethanol. The uncoated glass was also subjected to the disinfection cycles.

Samples were also stored under water for 13 days and then then tested. The coating retained its virucidal ability for SARS-CoV-2 (See Figure S10).

3.3 The Cu_2O/PU Film is Robust. The Cu_2O/PU film is not noticeably scratched when handled with tweezers, although it can be removed by heavy, deliberate scratching. Five samples of the Cu_2O/PU film on stainless steel were scratched through to the steel with a razor blade in an 11

× 11, 1 mm square grid and then an attempt was made to remove each of the 100 small pieces of coating with tape (ASTM cross-hatch test ASTM D3359). For three independent samples, on average only 2.4 of the 100 squares were affected, with a standard deviation of 0.8, corresponding to a 4B rating in the ASTM standard (See Figure S11). When tape was used to pull off the top layer of particles from an unscratched sample (a variant of ASTM D1876 Peel test[19]), there was a 0.25% loss of coverage (p = 0.007, six samples); visual inspection of the images showed that only a few particles were removed (see Figure S12). These results indicate that the film has durability.

3.4 A Coating of a Cationic Polymer Coating Did Not Speed Inactivation of SARS-CoV-19. Two cationic polymer films were examined. A Film of PA (mainly primary amines) and a film of PDADMAC (quaternary ammonium). Both films were designed such that the polymer retained flexibility. The PA was tethered by covalent linkages and prior force measurements showed that chains could extend up 200 nm from the solid in solution.[5] PDADMAC chains could extend up to 10 nm from the solid.[13] This chain flexibility was designed to assist contact with a larger area of the curved virus. The cationic coatings did not, however, lead to greater inactivation of the virus for the first 24 h for PDADMAC or for the first 48 h for PA (See Figures S13 and S14).

4. CONCLUSIONS

A porous coating of Cu_2O/PU causes a swift and dramatic reduction of the infective titer of SARS-CoV-2. After one hour, a typical reduction is 99.9% compared to the uncoated sample. The coating retains its potency after multiple exposures to virus followed by washing with 70% ethanol in water, or after immersion in water for 13 days. The coating retains its mechanical integrity after being cut with a razor blade. Amine and ammonium-based polymers did not inactivate the virus under the conditions tested.

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Supporting Information

Figure S14. Viral titer for PDADMAC.

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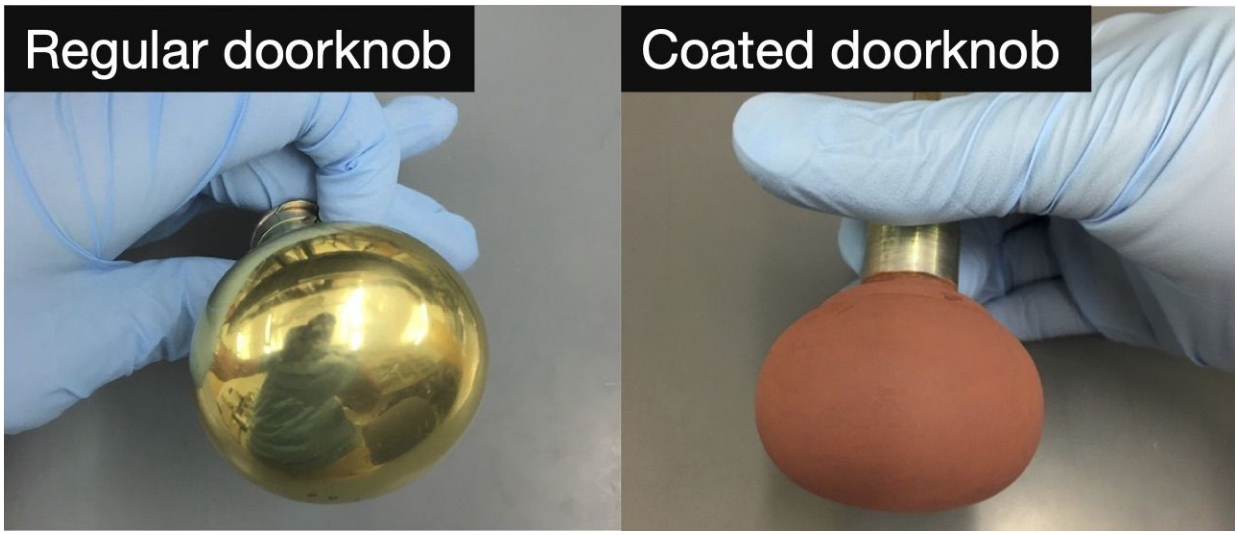
Table of Contents Graphic


Regular doorknob
Coated doorknob