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Chapter

Antiviral Coatings as Continuously Active Disinfectants

Luisa A. Ikner and Charles P. Gerba

Abstract

Antimicrobial surfaces and coatings have been available for many decades and have largely been designed to kill or prevent the growth of bacteria and fungi. Antiviral coatings have become of particular interest more recently during the COVID-19 pandemic as they are designed to act as continuously active disinfectants. The most studied antiviral coatings have been metal-based or are comprised of silane quaternary ammonium formulations. Copper and silver interact directly with proteins and nucleic acids, and influence the production of reactive free radicals. Titanium dioxide acts as a photocatalyst in the presence of water and oxygen to produce free radicals in the presence of UV light or visible light when alloyed with copper or silver. Silane quaternary ammonium formulations can be applied to surfaces using sprays or wipes, and are particularly effective against enveloped viruses. Continuously active disinfectants offer an extra barrier against fomite-mediated transmission of respiratory and enteric viruses to reduce exposure between routine disinfection and cleaning events. To take advantage of this technology, testing methods need to be standardized and the benefits quantified in terms of reduction of virus transmission.

Keywords: disinfection, virus, coating, continuously active, fomites

1. Introduction

Enteric and respiratory viruses can potentially be transmitted via contaminated environmental surfaces [1, 2]. Infectious viruses present on fomites may be transferred to the fingers and/or hands when touching various surface types under a broad spectrum of environmental conditions [3]. Transfer efficiency is affected by factors including virus species, inoculum size, and skin condition [4]. Subsequent contact with the eyes, nose, or mouth with contaminated fingers and hands may then provide access to susceptible human hosts [5]. Disinfection of environmental surfaces lowers the numbers of infectious microorganisms, thereby reducing the risk for transmission [6, 7]. However, such surfaces are subjected to continuous recontamination events, particularly in high-traffic areas and facilities including hospitals, daycare centers, schools and office buildings where fomites are more likely to serve as reservoirs of pathogens [8–10].

There are hundreds of liquid-based formulations that are registered as disinfectants with governmental regulatory agencies around the world, and a subset of those also carry label kill claims against non-enveloped and enveloped viruses. The efficacy testing that is required for the issuance of product label claims is performed using internationally-recognized standard test methods such as those produced by

the American Standard for Test Materials (ASTM) and the European Standard (EN), among others. Liquid disinfectants can be applied to hard, non-porous surfaces using spray devices, towelettes (wipes), or as bulk liquid volumes to address large, soiled areas. To achieve the antiviral inactivation claims specified on product labels, disinfectants must be used according to the manufacturer's instructions which may require maintaining a completely wetted surface for up to 10 minutes. However, the habits and practices of product users are contrary to the directions specified on the label. A recent survey of American adults conducted on behalf of the American Cleaning Institute in 2020 revealed that 26% of respondents adhere to label directions during household disinfection routines; however, an equal percentage of those surveyed did profess to wiping surfaces until dry immediately after spraying with no adherence to contact time instructions [11]. An additional 16% of respondents claimed to use a single-pass method for disinfectant wipes rather than the multiple passes that are generally required to maintain surface wetness for several minutes.

The importance of correct disinfection usage has been of increased concern during the COVID-19 pandemic. Alternative disinfecting surface treatments that are capable of inactivating infectious agents, in particular viruses, are under research and development [12, 13]. A number of new and diverse antiviral coatings and films have been synthesized, and fixed or immobilized applications including solids (e.g., antimicrobial plastics), paints, and metals are increasingly of interest for their antiviral capabilities. The factors affecting virus survival and the efficacy of antiviral

Factor	Impact
Type of virus	Non-enveloped viruses are generally more resistant than enveloped viruses
Relative humidity	Drying rates of deposited viruses are affected, impacting viability
Temperature	Protein denaturation results in loss of structural integrity of virus
Soil (dirt) load	Increased demand on antiviral actives, decreasing availability for virus inactivation
Coating composition	Mechanisms of antiviral action differ among viruses and vary according to formulation
Contact Time	Time required for at least a 99.9% (3 $\log_{10}$) reduction in titer may range from minutes to hours

Table 1.
Factors that affect virus survival and efficacy of antiviral coatings [2, 14].

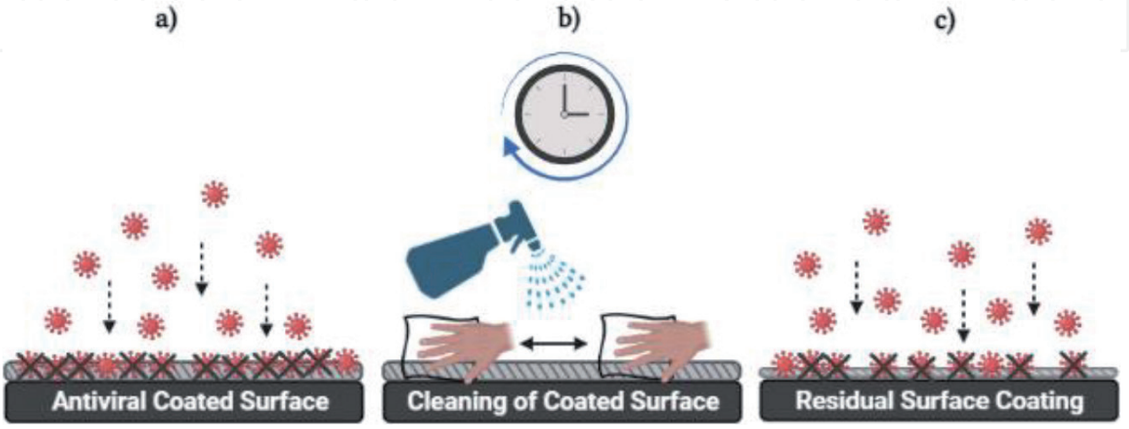

Figure 1.
Continuously active antiviral surface coatings: a) coating applied to hard, nonporous surface demonstrates antiviral activity following virus deposition; b) coated surfaces are cleaned/disinfected with wiping action with passage of time, c) residual coating demonstrates continuous antiviral efficacy following surface cleaning events (Created in BioRender.com).

coatings have been reviewed [2, 14] and include virus structure (i.e. enveloped, non-enveloped), the presence of organic soil (dirt), temperature, relative humidity, coating composition, and contact time (**Table 1**). The ability of treated surfaces to remain continuously active after repeated cleanings and use of liquid disinfectants is also critical (**Figure 1**). Unfortunately, there are no generally accepted methods for evaluating anti-viral surface coatings, making it difficult to compare the efficacy of different materials and studies. More research is warranted to better understand breadth of antiviral efficacy of these novel disinfecting technologies, and whether they can exact measurable and meaningful impacts on public health.

2. Continuously active disinfectants applied to hard, nonporous surfaces

A number of formulations have been developed and assessed over the past two decades that are capable of antiviral inactivation for extended periods of time following surface application (**Table 2**) [12–16]. Such applications have been considered as continuously active disinfectants and impart self-disinfecting properties to treated surfaces. There are many industry-based and third-party contract laboratory studies that have evaluated the antiviral properties of these surface treatments. However, few have been published to-date in peer-reviewed scientific journals [17], with an even smaller subgroup assessing efficacy against infectious viral agents. Continuously active disinfectants are generally evaluated for residual inactivation efficacy using a controlled, standardized wear and abrasion procedure such as that described in United States EPA Protocol #01-1A [18]. Briefly, a product applied to a hard non-porous surface is subjected to alternating dry and moistened wiping procedures over a specified time period ($\geq$ 24 hours) with intermittent reinoculations of the test organism. A minimum of 12 wear cycles is required, and the remaining film of test product is challenged by a final dose of the target organism ($\geq$ 4.8 $\log_{10}$) for up to 5 minutes of contact time. Residual efficacy depends in part on the amount of disinfectant remaining on the surface after the wear and abrasion testing which indicates its durability. Products that are readily removed from surfaces during repeated wet and dry wiping events could require regular reapplication to ensure proper performance against target microbes. As with standard disinfection,

Coating*	Type of viruses tested against†,‡	Mechanism of inactivation
Silane polymer QAC	Influenza, HCoV-229E, SARS-CoV-2, feline calicivirus	Behaves as a surfactant; disrupts lipid and protein structure
Copper	Influenza A, hepatitis A, feline calicivirus, adenovirus, HCoV- 229E, SARS-CoV2	Reactive oxygen species; protein and nucleic acid denaturization
Silver	Influenza, SARS-CoV2, HCoV-229E, murine norovirus	Reaction with sulfhydryl groups in proteins; prevention of viral attachment to host cells
Zinc	Murine norovirus, SARS-CoV-2, influenza	Inhibiting proteolytic cleavage, preventing synthesis of viral polypeptides
Titanium dioxide	Influenza, adenovirus; SARS-Co-2	Generation of reactive hydroxyl radicals

**QAC: quaternary ammonium compound.*
†HCoV-229E: human coronavirus 229E.
‡SARS-CoV-2: SARS-related coronavirus 2.

Table 2.
Common antiviral surface chemistries and mechanisms of action [12–16].

residual effectiveness generally follows the hierarchy of susceptibility of viruses to disinfectants, where enveloped viruses are more susceptible to inactivation than non-enveloped viruses [19].

Quaternary ammonium compounds (QAC) have been in general use by industry and consumers for almost 70 years, mostly as rapid-action (≤ 10 minutes contact time) spray disinfectants for contaminated surfaces. They are considered as cationic surfactants or detergents, and are highly effective at disrupting the inner membranes of bacteria and lipid bilayers of enveloped viruses. QAC have undergone formulation changes to enhance effectiveness against non-enveloped viruses [20]. When combined with silane and polymers, they can be applied as a surface coating with antimicrobial properties [21]. Silane-QAC are long-chain molecules comprised of three principal components: 1) a silane base for covalent bonding to surfaces; 2) a centrally-located positively-charged nitrogen component, and 3) a long chain 'spear' consisting of a methyl hydrocarbon group. They can be applied to hard surfaces and to fabrics, and their virucidal efficacies may persist from 24 hours to weeks on treated surfaces.

Peer-reviewed studies evaluating the effectiveness of QAC-based surface coating treatments against viruses are currently limited. A quaternary ammonium polymer coating applied to stainless steel coupons demonstrated greater than 99.9% (>3 $\log_{10}$) reduction during 2 hours of contact against SARS-CoV-2 and human coronavirus 229E in the presence of 5% organic soil, although wear testing was not performed to assess residual antiviral activity [22]. Another study evaluating a QAC applied onto acrylic surfaces against subsequent SARS-CoV-2 and human coronavirus 229E contamination events demonstrated rapid inactivation upon contact (>90% [>1 $\log_{10}$] reduction); however, just one cleaning event of the coating using a water-based detergent and microfiber cloth substantially reduced product efficacy [23]. More peer-reviewed research is needed to better understand the breadth of QAC coating efficacy against the spectrum of non-enveloped and enveloped viruses, and under varying soil load and environmental conditions. Additional studies are also warranted to assess the durability of these coatings following simulated touches and cleaning events, and the resulting impacts on antiviral effectiveness.

3. Titanium dioxide

Titanium dioxide (TiO_2) is a photocatalytic inorganic chemistry that can be applied to a wide variety of surface types to provide antiviral protection. It does not inactivate viruses directly, but acts as a catalyst in the presence of UVA light (wavelength 315 to 400 nm) to generate reactive oxygen species that cause structural damage to viruses. The presence of moisture (in the air or on the surface) and oxygen are necessary for TiO_2 to be an effective antiviral agent. Light intensity is also key in driving the photocatalytic reaction. Residual photocatalytic activity may also occur in the dark after exposure to UV light, but is dependent on the prior exposure intensity.

Most of the studies evaluating the antimicrobial effectiveness of TiO_2 have focused on bacteria, and data on viruses remains scant in the literature [16]. TiO_2 has demonstrated >3 $\log_{10}$ reduction against influenza A within 4 hours, and > 1 $\log_{10}$ inactivation of feline calicivirus within 8 hours [24]. TiO_2 coatings have also been modified with fluorine to increase the production of reactive oxygen species under the low UVA-intensity fluorescent lighting that is typically found within indoor settings. Bacteriophage MS2, feline calicivirus, and murine norovirus infectivity levels were reduced by 2.6, 2.0, and 2.6 $\log_{10}$, respectively, on fluorinated TiO_2

surfaces [25]. The antiviral action of TiO_2 can be further enhanced within indoor environments by the addition of metals [26, 27]. A 1% silver-amended TiO_2 formulation yielded >4.00 log_{10} reduction of influenza A and enterovirus following a 20-minute exposure in the presence of a low intensity (15 W) UVA lamp [28]. More recently, infectious SARS-CoV-2 was reduced to levels below detection on TiO_2 and TiO_2-Silver (Ag) ceramic-coated tiles within 5 hours of exposure [15].

4. Metals

Metals such as copper, silver, and gold have been recognized since ancient times as having some health benefits, and the antibacterial properties of metals have since been well-studied [29]. In contrast, the mechanisms of metal inactivation of specific viruses remain unclear, although a number have been proposed and evaluated. Certain metals in trace amounts are critical to the function of viral proteins and genetic processes; however, levels in excess cause structural damage and affect viability [14]. The presence of these metals stimulates the generation of reactive oxygen species and damages viral envelopes as well as nucleocapsid proteins [30]. Metals can be incorporated into plastics and fabrics, used as actives in coating formulations, and fashioned directly into surfaces for direct use (e.g., copper sheets for incorporation into high-touch surfaces).

4.1 Copper

The antimicrobial properties of copper have been extensively studied, with efficacy demonstrated over a broad range of temperature and humidity values [1]. The proposed antiviral mechanisms of solid-state copper, copper oxides, and copper alloys against enveloped and non-enveloped viruses have been thoroughly reviewed [31]. Copper (I), (II), (III) ions act directly by denaturing viral surface proteins, and indirectly by the formation of reactive oxygen species that damage viral RNA and DNA. Copper surfaces inactivated infectious influenza A (H1N1) within 6 hours by 3 to 4 log_{10}, relative to virus levels remaining on stainless steel coupons [32]. Although copper has demonstrated broad-spectrum antimicrobial activity, it may be impractical to replace bulk materials within high-traffic areas (e.g., clinical settings) with copper products or components. The recent development of cold- and thermally-applied copper sprays, as well as fixed copper nanoparticle coatings and paints, enables continuously active disinfection measures against a spectrum of viruses [16]. Copper nanoparticles in the oxide form have shown promise against herpes simplex virus, human norovirus, and influenza A (H1N1) [31]. When applied using the cold spray technique, copper nanoparticles reduced infectious influenza A virus particles to levels below detection within 10 minutes [33].

4.2 Silver

The antimicrobial properties of silver have been known for more than a century. Much of the research investigating the antimicrobial properties of silver has examined inactivation in suspension, where lower doses are required to achieve inactivation effects relative to other metals [34]. Silver binds with disulfide (S-S) and sulfhydryl (-SH) groups in proteins, facilitates the production of reactive oxygen species (e.g., free radicals), and is believed to inhibit entry of HIV-1 into CD4+ host cells [35]. Unlike copper, the efficacy of silver decreases markedly at relative humidity levels <20% [1], and solid-state silver appears to be much less effective against

bacteriophage Qβ and influenza A than solid-state copper [36]. For surface applications, silver nanoparticles have been extensively researched. Silver nitrate and silver nanoparticles in surface coatings reduced recoverable levels of feline calicivirus and murine norovirus for up to 150 days [37]. Silver has also been incorporated into fabrics (hospital gowns, pillowcases, cotton sheets), textiles, and membranes, demonstrating antiviral properties against feline calicivirus and murine norovirus, as well as enveloped viruses [16, 38].

4.3 Zinc

The antiviral properties of zinc have been researched for the past several decades. Zinc inhibits proteolytic cleavage and the synthesis of viral polypeptides by human rhinovirus [39], and interferes with polymerase function and protein production by herpes simplex virus 1 [16]. For surface applications, pure zinc, itself, does not exhibit high levels of antiviral activity. A 1 $\log_{10}$ reduction of murine norovirus on pure zinc was measured within 2 hours, relative to complete inactivation of the test virus via synergism when exposed to a copper-silver-zinc alloy [40]. On plastic coupons with incorporated silver/copper-zeolites, >1.7 $\log_{10}$ and > 3.8 $\log_{10}$ reductions were achieved for human coronavirus 229E and feline calicivirus, respectively, within 24 hours [41]. More recently, zinc ion-embedded polyamide fibers were found to reduce levels of infectious influenza A and SARS-CoV-2 by approximately 2 $\log_{10}$ within 30 minutes [42].

5. Novel antiviral surface treatments

Research efforts are ongoing for the development of novel and continuously active coatings that are capable of maintaining low levels of bioburden while inactivating pathogenic microorganisms. A thorough review has been published of these coatings and their proposed mechanisms of action [14, 43]. The antiviral actives include biopolymers (e.g., antimicrobial peptides), synthetic polymers (e.g., polyethyleneimines, and graphene [14, 44, 45]. Natural product-based surface coatings and super-hydrophobic surfaces are also under development [46, 47]. Although many of these innovative technologies demonstrate promising antiviral effectiveness, further assessments of efficacy against additional types of viruses under various conditions are required. Reproducibility data generated among different lab groups would also be ideal to ensure product efficacy and reliability. Further, scaling up from the lab bench to assess these technologies under real-world conditions (i.e. placement into high-traffic, high-touch areas) will provide insight as to the consistency of their efficacy.

6. Conclusions and recommendations

From this review, it is clear that promising antiviral continuously active disinfectants are a reality. However, many obstacles exist before their widespread implementation. These include:

- Development and validation of standard methods for testing the efficacy of antiviral continuously active disinfectants. Ideally, these methods would indicate appropriate experimental conditions including relative humidity and temperature, organic soil load matrices, and evaluation of virucidal efficacy against enveloped and non-enveloped viruses.

- Establishing an acceptable contact time for a 3 $\log_{10}$ (99.9%) decrease in infectious virus. Some continuously active disinfectants can achieve this goal within a few minutes, and others may require 1 to 2 hours.

- Demonstration of the reduction in illnesses within facilities in which continuously active disinfectants are used. This is an ideal requirement, but difficult to achieve because of the high cost and multiple routes by which enteric and respiratory viruses can be transmitted. Reductions in hospital-acquired infections have been demonstrated with the use of copper [48–49] and silane QAC [50] disinfectants, but such studies are not always ideal because of limitations inherent in epidemiological studies, and extracting precision is usually lacking. Further, more information is needed as to the potential human health and environmental impacts of silane QAC usage in these settings.

- Application of quantitative microbial risk assessment (QMRA) to quantify the cost/benefits of continuously active disinfectants. QMRA is a lower-cost approach to documenting the probability of disease reduction that can be achieved. It can be used to estimate the difference in benefits from a continuously active disinfectant that inactivates 99.9% of the virus within 1 minute vs. one that achieves this within 2 hours.

- Education of regulators, public health officials, and the general public is necessary to ultimately achieve the benefits of continuously active disinfectants. There is concern that their use may provide a false sense of security, causing consumers to clean and disinfect less frequently. Continuously active disinfectants should be looked upon as an additional barrier, and not as a replacement for routine cleaning and disinfection.

Conflict of interest

The authors have no conflict of interest to declare.

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