

Benchmark

Inhaler with electrostatic sterilizer and use of cationic amphiphilic peptides may accelerate recovery from COVID-19

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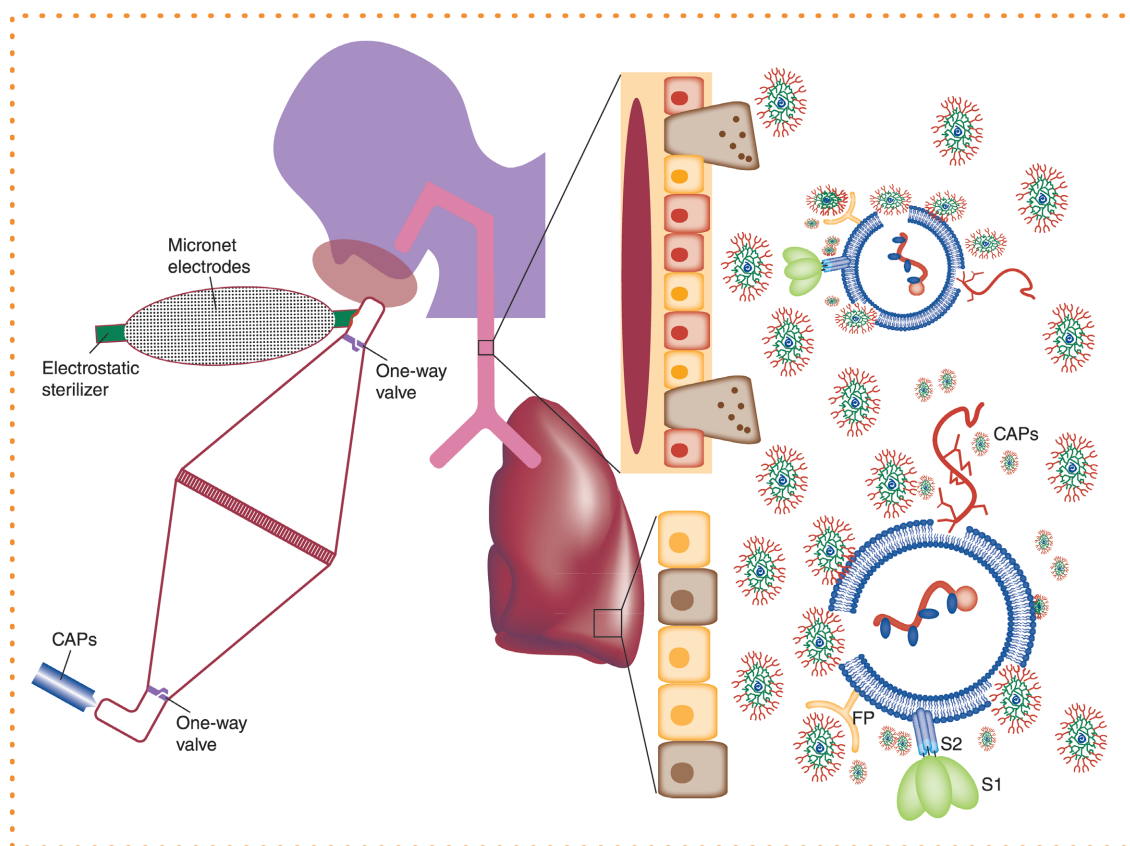
ABSTRACT

We explore the design of a smart inhaler with electrostatic sterilizer and propose the utilization of cationic amphiphilic peptides, independently or in conjunction with a bronchodilator, for COVID-19 patients to quickly improve wellbeing while maintaining a strategic distance to protect healthcare personnel from virus-containing aerosol or droplets during the process of inhalation.

METHOD SUMMARY

We have designed an economical smart inhaler which includes electrode-based sterilization to kill the virus particles within droplets or in exhaled air with a spark, burning them instantly. We describe the introduction of CAPs separately or in combination with a bronchodilator for COVID-19 patients to reduce the viral load in the respiratory tract and promote fast recovery.

GRAPHICAL ABSTRACT



KEYWORDS:

CAPs • COVID-19 • electrode-based sparking • smart inhaler • virus sterilization

The pandemic of COVID-19, a severe acute respiratory syndrome caused by coronavirus SARS-CoV-2 infection, is a global concern. A coronavirus has four significant supporting proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein and the envelope (E) protein [1]. The N and M proteins are responsible for host cellular response to viral infection by manufacturing the nucleocapsid and the shape of the viral envelope, respectively [2]. Coronavirus enters into the host cell using a homotrimeric transmembrane spike (S) glycoprotein on its surface [3]. The S protein contains two functional subunits: S₁ is responsible for binding to the host cell receptor molecule (angiotensin-converting enzyme 2, ACE2) and the S₂ subunit mediates the fusion of viral and cellular membranes [4]. The S protein is additionally severed by host proteases at the S₂' cleavage site found upstream of the fusion peptide [4]. This intricate procedure is important for promoting virus–cell fusion. The smallest auxiliary protein, E protein, abundantly expressed into the infected host and significant for intracellular trafficking, additionally participates in the development of the virion envelope [5].

The structure of E protein includes a 25–amino acid exceptionally hydrophobic transmembrane domain alongside a hydrophilic carboxyl-terminal region. The hydrophobic region of the transmembrane domain contains one amphipathic α -helix responsible for ion conductive pore development in membranes [6]. The S₁ receptor binding unit and an S₂ membrane fusion unit of the S protein ties to the hotspot on human ACE2, making a salt scaffold, particularly in hydrophobic conditions. Additionally, two hydrophobic (heptad) repeat regions, HR1 and HR2, are found near the membrane anchor, a significant characteristic of class I viral fusion proteins [7]. Strikingly, the membrane fusion mechanism is promoted by two SARS fusion peptides which strongly perturb the structural integrity of anionic vesicles by counteracting the arch weights on phosphatidylethanolamine membranes. The combination/fusion protein assists with expanding the anionic nature of the membrane by simultaneously causing an increase in the lipid-packaging process and a decrease in the intramembrane water content [8].

In this context, it is conceivable that the passage of infectious particles could be diminished by modifying the hydrophobic microenvironment. The negatively charged phospholipid bilayer helps the assembly of viral proteins – including E protein – for budding, envelope arrangement, and pathogenesis [9]. A cationic amphiphilic peptide (CAP) surfactant might be generally appropriate to neutralize the environment and reduce viral passage; the cationic nature of surfactant not only prevents the possibility of frothing, but also strengthens links with the negatively charged viral membrane envelope. It also lessens the electrostatic charges of the S protein and helps to reduce the affinity of the S protein for the ACE2 receptor.

CAPs can change the microenvironment in lungs & respiratory tract of COVID-19 patients

CAPs are known effector molecules synthesized in the host cell in response to immunological challenge by pathogens, and can eliminate microorganisms (bacteria, fungi and protozoan parasites) and acellular entities (viruses and viroids) [10]. The epithelial surfaces of the respiratory tract and lungs are shielded from pathogens by emitting safeguarding molecules, referred to as intrinsic mucosal resistance. This intrinsic mucosal resistant framework eliminates pathogens by forestalling their colonization in the epithelial layer. Synthesis and discharge of a few CAPs – for example, collectin, β -defensins, cathelicidins, hydrophilic surfactant proteins – and other molecules plays a significant role in counteracting pathogen attacks [11]. CAPs have an expansive range of action against microorganisms and infections, neutralize endotoxins and exhibit other *in vivo* activity [12]. The utility of recombinant lung surfactant proteins has been demonstrated for the treatment of respiratory pain disorder in neonates, chronic obstructive pulmonary disease, emphysema, cystic fibrosis and asthma [13]. Both *in vitro* and *in vivo* data reveal the significant impact of CAPs in epithelial host defense [14]. Under inflammatory disease conditions, illness and morbidity are enhanced because of dysfunction in mucosal resistance [15]; hence inhalation of CAPs or hydrophilic surfactant proteins should be an effective way to deal with receptor-binding proteins of viruses, interrupting or disrupting the membrane lipid bilayer or annihilating colonized virus particles from the epithelial surface.

CAP-induced disturbance/disruption of the membrane lipid bilayer could happen in various ways, as envisaged in various studies (e.g., barrel-fight model, toroidal model, cover model and cleanser model) [16,17]. A few CAPs are notable for causing fusion of cell membranes and can control viral infections by intervening in the fusion process between the host cell membrane and the enveloped virus [18]. The fusogenic TAT protein transduction area has been utilized to convey a wide scope of the naturally dynamic segments and medications by the immediate entrance over the lipid membrane [19]. Membrane permeabilization is viewed as a significant trait of antiviral action. In poxviruses, rifampin is a compelling inhibitor of viral envelope arrangement; lipid layer-bound viral proteins might be targeted immunologically to expand its counterviral efficacy.

For a successful and effective interaction, both electrostatic charge and hydrophobicity are significant. A positive charge is required initially to attract negatively charged membranes, and hydrophobic mass aides is required to disturb the membrane just as it makes contact with the hydrophobic site of HR1, HR2 area of viral combination protein and the receptor restricting space of S protein; this may lessen viral passage into the cell. The significant point here is that higher hydrophobicity increases hemolytic activity, which may hinder the utilization of CAPs. In any case, hemolytic action might be diminished by the alteration of residues [20]. A few lipopeptides, including maginin and gomesin, are known to be successful CAPs for antimicrobial action. Nonetheless, the use of CAPs is managed here through an inhaler, allowing the CAPs to reach to the upper respiratory tract and lungs, which are the hotspot for SARS-CoV-2 because of their overwhelming hyperexpression of its main receptor molecule, ACE2. Their cationic property is apt to disrupt the viral

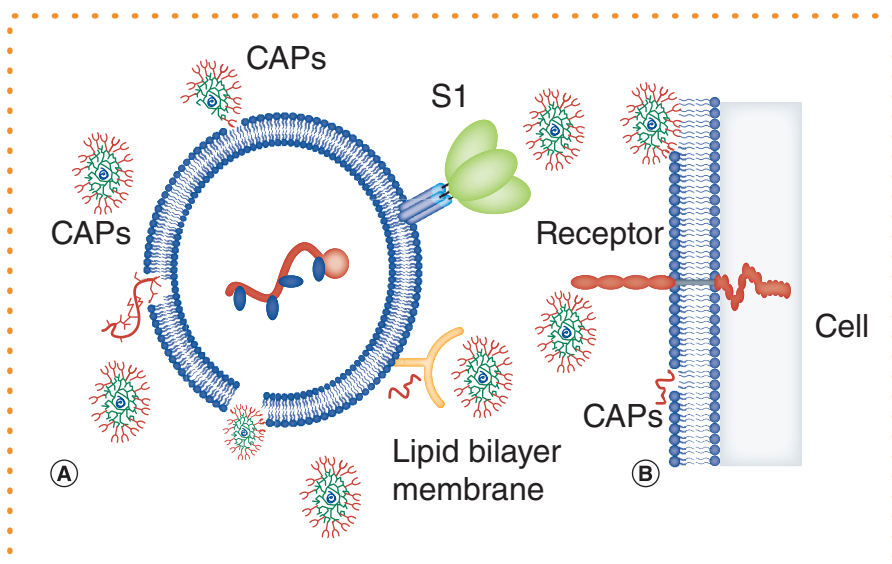


Figure 1. Schematic representation of the CAP molecule's interface and interaction with a virus particle. The illustration shows a representative schematic structure of SARS-CoV-2 with lipid bilayer showing the spike protein (S1) along with fusion protein. (A) Possible self-assembled peptides (in micelle form or native helix form) can bind directly to the highly anionic membrane as well as to hydrophobic surfaces such as fusion protein, S protein and E protein of the virus. (B) Similarly, the micelle may also bind to ACE2 or membrane of the host cell.

lipid bilayer membrane, and their amphiphilic nature can permit hydrophobic particles to be solubilized in liquid by shaping micelles. Additionally, the hydrophobic nature of the peptide has a tremendous affinity to bind nonspecifically with the profoundly hydrophobic fusion protein, E protein and S protein of SARS-CoV-2. It can change the milieu by the arrangement of the micelle; a few intact molecules may likewise tie to the hydrophobic area of the fusion peptide, E protein or spike protein of SARS-CoV-2 by hydrophobic collaboration or van der Waal forces (Figure 1) [21].

Design of a smart inhaler for COVID-19 patients

The inhaler is an extremely common and valuable device for conveying medicine into the body via the lungs, and is commonly utilized for the treatment of asthma, chronic obstructive pulmonary disease and viral diseases. COVID-19 patients often display symptoms of extreme respiratory complication and inhalers may be used to provide immediate relief. Healthcare workers may risk infection from patients using inhalers and none can rule out the possibility of spreading contamination in the room during exhalation. Here we have designed a unit to stop the spread of virus particles from patients. The inhaler is commonly utilized for quick alleviation of blocked airways. Although it delivers short-acting medications, during its use aerosolized viral particles may be released into the environment and may affect health workers. For this reason, another device is proposed to kill viral particles inside the aerosol of COVID-19 patients while inhaling air (Figure 2).

Working principle & using process

To assemble the gadget, the two halves of the spacer need to be firmly pushed together to rotate the mouthpiece top. The spacer includes two locks which guarantee proper assembly of the two parts. A canister is put into the face of the inhalation chamber with one push. There is a one-way gate valve (OWGV) which helps entry of the medicine during inhalation but does not let it out in this entryway. The full inhalator air is flown in this gadget and followed to the mouthpiece. There is another OWGV in the guard of the face of inhalation chamber. The pressurized canned products from exhalation are not returned to this valve, which will be shut due to the OWGV working head.

The patient exhales completely, closing the lips immovably around the mouthpiece to make a good seal without biting on it, breathes in profoundly through the mouth, and in this manner takes in the medicine through the spacer. At that point, the patient removes the inhaler spacer from the mouth, holds the breath for about 10 s (or as long as possible) and breathes out gradually. A different parabolic chamber is attached with this gadget, where one cathode plate and one anode plate are placed independently. A high efficiency particulate air channel, battery, switch and other devices creating a high voltage circuit are additionally appended. A push switch is arranged outside of the parabolic chamber. An ordinary 4 V direct current (DC) battery is utilized in our device to create a high intensity power of 1000 V to enable the positive anode and negative cathode free to liberate charged particles separately. A negative voltage of 1000 V is applied between the cathode wire or plate. An electric discharge from the anode plate ionizes the air; aerosol concentrates around the electrode inside the parabolic chamber during the utilization of high voltage. This is then ionized, causing sparking-induced burning of virus particles due to huge electrostatic power. Viruses in the inhaled air or aerosols within the gadget are killed instantaneously, and is

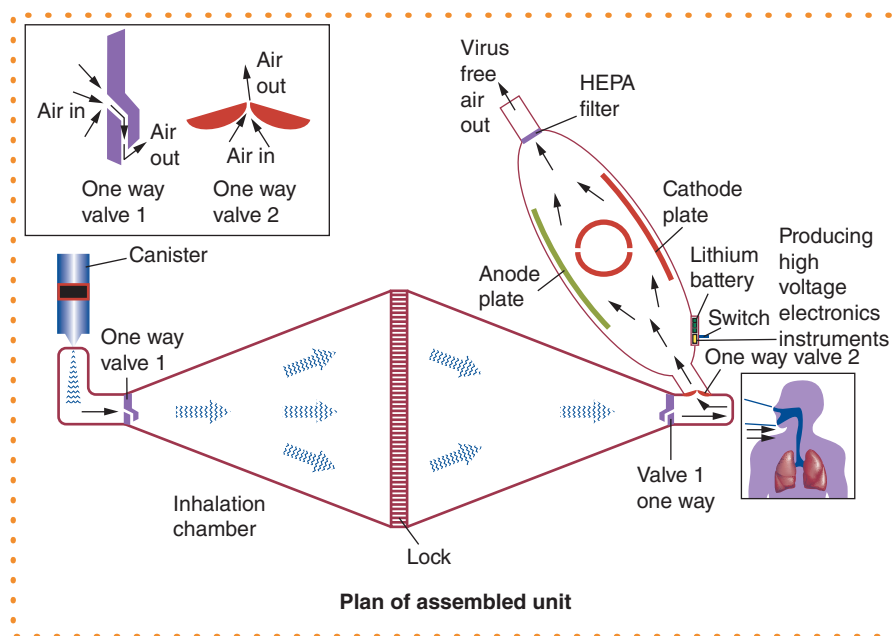


Figure 2. Schematic representation of the proposed smart inhaler with electrostatic sterilizer.

burned right away inside the device. When patients breathe out slowly, the OWGV will open and air goes into the parabolic chamber. This inletting air is charged by cathode and anode electrodes, leaving virus particles to be burned. At that point the charged air flowing through the channel can trap 99% of remaining virus particles. Virus-free air will be discharged from the chamber, preventing dissemination of viruses.

Two strategies are proposed here for COVID-19 patients. First, CAPs might be brought into the inhaler or medicine independently, alongside bronchodilators and may assist with diminishing the interaction propensity between ACE2 receptors and the S1 protein of SARS-CoV-2. The virus is mainly abundant in the lung and respiratory framework. After inhalation of CAPs, viral membranes rupture and the resulting new molecular membrane arrangement should be disordered; this should loosen binding with ACE2 receptors and diminish the viral burden. Second, another plan of smart inhaler has been proposed for COVID-19 patients. We have appended an extra parabolic chamber with battery-operated terminals to kill viral pathogens within a second by electrical contact. In this way, the risk of contaminating healthcare personnel with virus-loaded aerosols released from the exhaled air is diminished.

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