Combination Drug Delivery Strategies to Target Anti-Viral and Anti-Inflammatory Compounds to the Lungs of COVID-19 Patients

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Abstract

The current COVID-19 pandemic which is caused by the severe acute respiratory syndrome (SARS) corona virus (CoV)-2 (SARS-CoV-2) has infected more than 50 million people and more than 1 million deaths worldwide, with over 250K deaths in the United States alone1. The major route of transit/access for the virus into the human body is via the nasal and airway route resulting in the lungs being the primary organs of destruction. The virus is known to bind to the angiotensin converting enzyme (ACE2) receptors that are highly expressed in the human airways and also on the surface of pulmonary immune cells especially the alveolar macrophages (AMs)2. This viral fusion with the ACE2s is known to be the primary mechanism via which the SARS-CoV-2 fuses with the host cell and is considered widely to be the first step which is followed by the viral proliferation and cytokine storm.

keywords: Respiratory syndrome, drug delivery, Lungs, Patients.

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Introduction:

The major cause for death in COVID-19 patients is said to be acute respiratory distress syndrome (ARDS) which is primarily characterized by insufficient gas exchange in the alveolar region leading to suffocation and death. The insufficient gas exchange is in turn known to be caused primarily by the fluid infiltration into the alveolar space which is a direct consequence of the extreme pro-inflammatory cytokine secretion (commonly refereed to as cytokine storm) caused by the viral activation of alveolar macrophages and also other pulmonary immune cells. The excessive fluid infiltration is into the alveolar space is also capable of depleting the pulmonary surfactant in the alveolar region leading to alveolar wall collapse further exacerbating the breathing difficulties for the COVID-19 patients. Thus, the attachment of SARS-CoV-2 to the ACEs expressed on pulmonary cells and alveolar macrophages play a major role ARDS progression via fluid infiltration into alveolar space and pulmonary surfactant depletion3.

Therefore, it is evident that targeting a combination of anti-viral and anti-inflammatory compounds to the lungs of COVID-19 patients using an array of inhalation drug delivery strategies might be better suited to abate both the viral proliferation as well as cytokine storm simultaneously, compared to single therapeutic intervention and other routes of drug administration4. Such a combination drug delivery strategy to target multiple therapeutic moieties capable of controlling viral replication and inflammation might result in better clinical outcomes and decrease the chances of severe infections. The commonly used inhalation drug delivery strategies/dosage forms like pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs) and nebulizers can be investigated for their suitability for COVID-19 inhalation product development. The choice of the inhalation drug delivery platform would highly depend on the drug's physicochemical properties, regional lung deposition profiles achievable with the different dosage forms, patient inhalation maneuver compatibility with the chosen inhalation platform, and most importantly the effect of excipients on the viral proliferation and inflammation to name a few aspects.

Method:

The pMDIs employing hydrofluoroalkane (HFA) propellants might be a suitable choice to formulate micronized versions of both lipophilic and hydrophilic therapeutic compounds, thus offering an edge over the nebulizer formulations that are typically suitable for hydrophilic drugs. The other important advantage the pMDI-HFA dosage forms can offer is a completely excipient free treatment, mainly because most of the emitted HFA propellant(s) would completely evaporate upon actuation of the inhaler owing to their very low boiling point. Such an excipient free treatment can be said to negate any excipient related exacerbations on the clinical outcomes mainly because the effect of commonly used excipients in inhalation product development on the SARS-CoV-2 proliferation and inflammation needs to completely investigated. Especially, in the case of DPIs that can use significant amounts of lactose as drug carriers the effect of lactose as an energy source to the viral proliferation may need to be investigated before making a final conclusion. Similarly, in the case of nebulizer formulations the different buffering agents and preservatives added to the

formulation might need to be investigated for their effect on viral proliferation and inflammation.

Discussion:

From the perspective of formulating multiple therapeutic compounds for their combined targeted delivery to the lungs, all three commonly used inhalation dosage forms might be suitable. An important clinical consideration to make note of before choosing the inhalation dosage form is the breathing profiles and inspiratory force the COVID-19 patients can generate. It might be important to ensure that the chosen inhalation dosage form/ device platform is capable of resulting in optimum regional lung deposition when the COVID-19 patients inhale at their comfortable inspiratory flow rate. Especially it might be of immense importance to ensure that the chosen inhalation platform for the targeting of the combination drugs deposits drug doses in the peripheral alveolar regions sufficient enough to result in a safe and efficacious therapeutic effect. In conclusion, this letter aims to briefly outline the importance and benefit of inhibiting the multiple pathways the virus can utilize to exert its harmful effects via targeting of more than one therapeutic compound to the lungs of the COVID-19 patients.

The role of pH in SARS-CoV-2 infectivity – A brief perspective for COVID19 therapeutic intervention(s):

The SARS-CoV-2 is dangerous in a lot of ways, and one of those ways is because it is an expert in aerodynamics/sky diving/ paragliding – referring figuratively to its ability to enter human body via airborne aerosol droplets. Once it lands in the upper airways/nasal area it needs to "dock" itself (viral fusion process) to a membrane surface protein (ACE2) – just like a space shuttle trying to dock with a space station after its journey through space. This "docking" mechanism involves complex deformation of the viral spike protein in order to allow the physical fitting of the viral spike protein into "grooves" in the ACE2s probably.

That is where the amino acid composition of the viral spike protein comes into the spotlight. Like all proteins, the SARS-CoV-2 viral spike protein is also composed of several amino acids and thus the charge state of each of the amino acids that make up the viral spike protein would evidently have a role to play in viral fusion process with the host cell membrane via ACE2. The isoelectric point of the SARS-CoV-2, the individual ionization and charge states of the amino acids are prone to local pH changes – the pH of the biological fluid in which the virus can remain/land post inhalation. Alteration of the local pH can thus lead to protonation or deprotonation of the individual amino acids depending on their isoelectric points – which in turn can lead to the disturbance of the balance of forces (hydrogen bonding mostly) that are existing between these individual amino acids. The alteration of pH thus can lead to change in the net attractive and/or repulsive forces within the viral spike protein's amino acid population, ultimately affecting the deformation of the viral spike protein and its chances of fusion with the host cell membrane via ACE2s.

Conclusion and Recommendation

One of the key processes required for secretion of pro inflammatory cytokines is that the binding between major histocompatibility (MHC-I or II – depending on innate or adaptive immunity perspective) and the foreign antigen needs to take place, and this MHC-I or II -antigen complex is then displayed on the surface of the antigen presenting cell (APC) which is the triggering event to activate CD4+ or CD8+ cells leading to secretion of pro-inflammatory cytokines. However, the MHC molecule is initially attached to a chaperone protein when present inside the lysosome or late endosome and for the antigen to attach to the MHC complex the intra-lysosomal or intra-endosomal pH needs to be at around 4-4.5, and any local/intracellular pH alteration prevents the separation of the chaperone protein from the MHC molecule which in turn prevents the attachment of the antigen to the MHC molecule. This results in the MHC-chaperone complex getting displayed on the APC surface (instead of MHC-antigen complex) which leads to less effective activation of the CD8+ or CD4+ cells thus leading to inhibition of inflammation. It is possible that the conformational changes needed to happen in the chaperone-MHC complex (needed for separation of chaperone protein from MHC) within the endosome or lysosome is pH dependent and can happen only withing a specific pH range.

Result:

Therefore, the local biological fluid pH is a major player in the molecular events of COVID19 namely, SARS-CoV-2 fusion, replication and the resulting cytokine storm – thus opening the doors for therapeutic interventions that can manipulate the local biological fluid pH to abate the viral fusion process.