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Engineered Nano-In-Micro Drug Delivery Scheme Against Sars-Cov2: A Hypothesis

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Abstract:

In late 2019, a novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) evolved in Wuhan city of China, which rapidly surfaced across the globe conducing to the Coronavirus Disease 2019 (COVID-19) pandemic. The SARS-CoV-2 infection may progress from mild to severe and critically state, however a plethora of cases are either asymptomatic or mild. An excessive release of pro-inflammatory cytokines and chemokines delineates the severity of the disease and the condition is called as the cytokine storm. The multiplication of the virus and depletion of T cells up-regulates the macrophages and monocytes to generate the cytokine storm. Tremendous efforts are being made to unearth an effective and efficient therapeutic strategy to contain the pandemic. These attempts are focused on discovering a vaccine, virus elimination, interrupting the virus-host interaction

or host modulations and many of them have demonstrated good clinical prognosis. The delivery approach of a potential drug is also pivotal into the bargain. Drug administration off target will not only deteriorate the ability but also delay the mechanism of action of that molecule. Synthetic nanosilicates (Laponite XLG) nanoparticles possesses a dichotic charge that makes them a classic drug carrier for targeted and sustained drug release. However, drug delivery into the lungs using only nanosilicates may be ineffective, as these particles will be cleared off from the pulmonary passage due their Nano size. Therefore, a mucoadhesive polymer like chitosan may serve as a secondary carrier to the drug loaded nanosilicates and can deliver the molecules at the targeted biological site. This nano-in-micro drug delivery system may tailor the therapeutic modality of SARS-CoV-2 infection and establish good clinical outcomes.

Keywords:

COVID-19, drug delivery, nanosilicates, nano in micro system

Introduction:

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) emerged in December 2019 in China and rapidly surfaced remote areas in the world causing a deadly pandemic. Majority of COVID-19 cases are asymptomatic or mild and the disease advances to severe or critical phase characterised by hyper-inflammatory state in the body. This hyper-responsive pro-inflammatory immune response with elevated levels of cytokines such as IL-6, tumor necrosis factor (TNF), IFN-γ, IL-2 is named as cytokine storm. Cytokine storm is considered to be an irreversible phase causing alveolar collapse, hyalinisation, fluid accumulation in the blood leading to acute respiratory distress syndrome (ARDS) which may be accompanied by toxaemia, disturbances in coagulation cascade leading to septic shock, DIC or multiple organ dysfunction syndrome (MODS) in COVID patients[1]. A plethora of therapeutic pipelines are under investigations and trials that focuses on either inhibiting the virus, its receptor binding mechanism, replication process or minimizing the destructive effect of cytokine storm. Biotech and pharma industries are consistently working on repurposing existing drugs, drugs showing antiviral mechanisms, antibody therapy, drugs protecting the lungs, vaccines etc. and these compounds evidently showed promising results in ex-vivo and in-vivo studies[2]. However, these interventions needs detailed studies and trails to arrive at a particular conclusion. Indeed, a number of therapeutic options are under implementation and development or discovery of an effective and efficient drugs/agents are in the pipeline. This is achieved by exploring better delivery routes of molecules and enhancing their mechanism of action for a breakthrough to reduce the pandemic burden and save millions of lives. Despite the effectiveness and efficacy of a therapeutic drug in suppressing the virus and disease progression, departure from an ideal delivery mode may delay its action or decrease the quality of the drug leading to therapeutic non-compliance. Therefore discovering various drug delivery pathways is correspondingly important as a drug discovery that can offer specific direction toward its target. The purpose of the current hypothecation is to propose a new nano-in-micro based delivery system for local, controlled and sustained drug release into the pulmonary tree.

Hypothesis:

Synthetic nanosilicates (laponite XLG, BYK) as a Nano-Bio vehicle for a drug that will serve as a primary drug carrier and a polymer like chitosan microspheres as secondary carrier for

desired drug delivery into the pulmonary tree. This nano-in-micro based delivery system may improve clinical outcomes and reduce the burden of COID-19 pandemic.

Rationale of the Hypothesis:

Nano-sized particles due to their high surface ratio improves the drug interaction with tissues, drug stability and prolongs the duration of drug release etc. thereby performing a vital role in the health-care system[3]. Synthetic nanosilicates ($Na^{+}_{0.7}[(Si_8Mg_{5.5}Li_{0.3})O_{20}(OH)_4]^{-0.7}$) are disk-shaped dual charged particles with positive charge at the edge and negative charge at each face. This property enables a wide range of interactions between the particles and various molecules like drugs or proteins etc. Due to very small range of size of nanosilicates (20-50 nm diameter; 1nm width), these particles can be easily clear-off from the pulmonary tract by their rapid exhalation or clearance due to alveolar macrophages[4]. Hence, it may comprise the potential of nanosilicate carriers to deliver a drug locally and in a sustained manner. To overcome such demerits, a micro-based carrier for drug loaded nanosilicate can be used that will serve as a secondary carrier for nanoparticles. The nano-in-micro based drug delivery has been investigated by many researchers using chitosan, mannitol etc. and this mode of delivery has showed a promising approach in delivering molecules to lung bypassing the ciliary and macrophage clearance and releasing drug loaded nanoparticles at the desired site for local and sustained drug release. The use of micro-sized particles brings the aerodynamic size in between 1-5 um, which is required for a inhaled particle to reach at the desired site into the lungs[5,6]. Chitosan as a pulmonary drug delivery agent is always been a centre of attraction for many researchers due to its biocompatibility especially with cells in respiratory passage, mucoadhesive properties and it has been examined for drug delivery in many diseases[7].

Discussion and Conclusion:

The rising concern of COVID-19 pandemic, its treatment plan and discovery of a wide spectrum of molecules/proteins stresses the necessity of unique delivery system. Currently, the drugs against SARS-CoV-2 used for trails are administered orally or intravenously, resulting in a prolonged hospitalization period. Though many of the repositioned drugs, molecules clinically demonstrated better prognosis and reduced mortalities, there is a need of drug formulation as their target site is usually very complex. Therefore, control over the drug release would be a hallmark of the treatment. Pulmonary system as a drug delivery target for nanoparticles has been already investigated in other respiratory or systemic diseases[8,9,10]. The potential of nanosilicates for control and sustain drug release in the respiratory pathway has not been investigated until date. Nanosilicates causes sustain and local drug release up to four weeks unlike other polysaccharide based materials, which release the complete amount of drug maximum up to seven days. Nano size particles are advantageous as they can disperse uniformly within the alveoli to achieve their target. Nevertheless, a secondary carrier is required for nanosilicates to enter into the pulmonary tree to reach the desire site. This can be achieved using micro-sized polymers like chitosan that can act as a secondary carrier for nanosilicates causing sustained and controlled drug release at the target site. Thus, nano-in-micro based system for drug delivery in COVID-19 patients may be game changer. Such type of delivery systems reduces the side effects of the drug if any and provide a quick onset of action. An ideal drug delivery system would release the antiviral drug perpetually over a long duration to engender a desired effect.

Declaration of Conflict of Interest:

The authors declare that they do not have any conflict of interest associated with the manuscript. The authors did not receive any funding for the article.

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