Lung Delivery Systems to Optimize Pharmacotherapy of COVID-19: A Concise Review

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Authors’ contributions

This work was carried out in collaboration among all authors. The MGA and AGS collected the Information, and wrote the first draft of the manuscript. Authors ASA and IBI edited the article. All author read and approved the final manuscript.

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ABSTRACT

Background: COVID-19 is an ongoing viral pandemic caused by the SARS-COV-2 virus. Several drugs were repurposed for its management; however, most of these drugs were not ideal treatments by traditional methods of administration, whether given by injection or orally. This is due to many reasons including pharmacokinetic limitations or drug-induced adverse effects. There is an urgent need to develop these drugs to target the virus in the lung tissue through inhalation.

Objective: To address the gap in knowledge regarding efficacy and safety of pulmonary drug delivery of repurposed antiviral against COVID-19.

Findings: Ongoing trials for inhalable formulations of several drugs such as Niclosamide; Remdesivir, Hydroxychloroquine, and Azithromycin among others showed promising results.

Conclusion: The development of pharmaceutical forms for inhaled administration of antiviral and anti-inflammatory drugs is an important direction that needs more attention to achieve the optimal management of respiratory infectious diseases.

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1. INTRODUCTION

COVID-19 is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of the end of July 2021, about 200 million cases had been reported, with four million deaths. [1-4]. Among emerging potential treatments, drug repurposing is considered one of the best possible options to address this urgent unmet medical need for new drugs [5]. These repurposed FDA approved drugs were subjected to in vitro testing and showed promising results against SARS-CoV-2 [6-8]. However, clinical trials of most antiviral drugs demonstrated inconsistent results or limitations [9,10].

There is a gap in knowledge regarding the efficacy and safety of pulmonary drug delivery of repurposed antiviral drugs. The present study aimed to review the utility of developing a lung delivery system for antiviral drugs against COVID-19. It involves a literature review of academic databases such as Google Scholar, PubMed, Science Direct, Scopus, using relevant keywords: pulmonary drug delivery, inhalation, pulmonary route, antiviral drugs, and repurposed drugs by their names, hydroxychloroquine; lopinavir; remdesivir; azithromycin etc.

2. LIMITATIONS OF ANTIVIRAL DRUGS IN THE MANAGEMENT OF COVID-19

Most antiviral drugs against SARS-COV-2 demonstrated inconsistent results or limitations in clinical trials, the following are a brief explanation of representative drugs.

2.1 Remdesivir (RDV)

Remdesivir (Veklury) is a broad-spectrum antiviral drug that acts as an RNA polymerase inhibitor. It is currently the first FDA approved antiviral drug against COVID-19 and available as an intravenous injection formulations, which is not suitable for outpatients [11-15].

It has many adverse effects including severe bradycardia [16], ECG changes [17], anaphylaxis, liver, and renal toxicity [14]. It is metabolized very quickly in blood to yield (nucleoside analogue, GS-441524) which requires activation in lung cells. It solution contains an excipient, which is likely to accumulate in cases of reduced renal function [14].

2.2 Lopinavir/ritonavir (LPV/r)

Lopinavir (LPV) is an antiretroviral protease inhibitor and has been repurposed to manage COVID-19. It is available as a fixed combination with ritonavir (to improve oral bioavailability of LPV [18, 19]. LPV/r has variable bioavailability which is affected by food and the type of formulations. The volume of distribution (VD) after an oral dose is about 17 L and 98% bound to proteins in plasma [20].

A meta-analysis concluded no significant advantage of LPV/r in alleviating symptoms of COVID-19 [21]. Cattaneo et al. suggested that the protein-adjusted IC₅₀ values of LPV required to inhibit SARS-CoV-2 replication in plasma were 200-fold higher than the concentrations measured in blood samples obtained from COVID-19 patients [22]. The explanation for the ineffectiveness of the drug was the subject of several published studies [23]. Another critical limitation is that RTV (a potent inhibitor of cytochrome P450-3A4) is given in combination with LPV; therefore, a long list of interactions with other medications must be considered in COVID-19 patients [24].

2.3 Favipiravir

Favipiravir (FPV; T-705) is a modified pyrazine analogue. It is a broad-spectrum antiviral RNA-dependent RNA polymerase (RdRp) inhibitor. It was included in COVID-19 treatment guidelines in many countries [25,26].

FPV has non-linear pharmacokinetics (PK), demonstrated as a decrease in drug concentration after chronic administration. This may be explained by the auto-induction of certain CYP450 responsible for its metabolism [27]. Moreover, there is an ethnic variation in FPV’s disposition [28,29]. However, a PK study in critically ill COVID-19 patients who received the recommended dose of FPV demonstrated a low trough level (1 µg/mL) [30]. (recall low potency against SARS-COV-2, EC₅₀ 61.88 µM [8]. The lung-to-tissue level of FPV was estimated to be about 50% of that in the blood. These PK data suggest moderate drug access to lung tissues [31]. The drug has some adverse effects, including a rise in serum uric acid, liver enzymes, diarrhoea, nausea, vomiting, and tachycardia.

Keywords: COVID-19; antiviral drugs; pulmonary drug delivery; aerosol; niclosamide; remdesivir; hydroxychloroquine; azithromycin.
2.4 Hydroxychloroquine

Hydroxychloroquine (HCQ) is a 4-aminoquinoline derivative [34]. The drug received extensive interest and debate for its potential activity against COVID-19 [35]. The absorption of HCQ is extensively variable (~70%; range: 25 to 100%). HCQ is metabolized in the liver through CYP2C3, CYP 2D6, 2C8, 3A4, and 3A5 into active and inactive metabolites. Therefore, the genetic polymorphism of these enzymes would affect its blood level. About 20% of HCQ dose is excreted in urine unchanged; hence renal function is likely to affect its clearance [36]. HCQ has a narrow therapeutic range and moderate protein binding (about 50%), primarily with albumin [37].

An In vitro study suggested that HCQ suppresses trained immunity, which may be more productive to the antiviral innate immune response to SARS-CoV-2 [38]. Furthermore, lung acidosis may be induced by severe COVID-19. Ali et al. suggested that HCQ is not likely to provide a potent antiviral effect in severe cases of COVID-19. If indicated, it should be given as early as possible to optimize its use [39]. Another limitation of HCQ is potential QT prolongation and ventricular arrhythmia. Unfortunately, there has been no dose-response relationship study to accurately predict the association of HCQ drug level with this cardiac toxicity [40-42]. Moreover, the drug showed extreme variability in drug levels in COVID-19 patients.

To this end, using a nebulizer with an inhaled nanoparticle formulation to deliver medications directly to the primary site of infection may allow for more targeted and accessible delivery in hospitalized and non-hospitalized patients, as well as potentially decrease systemic exposure to the drug. Interestingly, formulation and evaluation of some inhaled antiviral, immunomodulators, natural products, and miscellaneous compounds are going on (Table 1). This review will focus on antiviral drugs.

3. PULMONARY DRUG DELIVERY

Pulmonary drug delivery has many advantages when compared to another route of administration. The human lung is highly perfused tissue along with a large surface area, which leads to high bioavailability with rapid onset of action of inhaled medication. These features make it an optimal route for the treatment of various pulmonary disorders including respiratory infections [43]. The therapeutic efficiency of inhaled drugs is limited by airway geometry, mucociliary clearance, and alveolar macrophages. Furthermore, the efficacy of inhaled medications may be influenced by where it is deposited in the respiratory tract, the dose administered, and pathophysiological alterations [44].

Numerous studies recognized that the administration through the lungs is more efficient for the management of respiratory infections. For instance, the established inhaled anti-infective drugs to treat viruses such as adenovirus, coronavirus, echovirus, influenza, respiratory syncytial virus [45].

3.1 The Rationale for Pulmonary Delivery of Antiviral Drugs

The SARS-CoV-2 virus induces a disease that mainly impacts the airways [1]. Consequently, identifying a repurposed drug to be administered via the pulmonary route represents an effective method of treating the disease. Such a method has been proven successful for treating other conditions affecting the lungs, possibly due to its quick action, low metabolic activity at the site, and decreased likelihood of harmful outcomes [43-45]. Therefore, this study seeks to highlight candidate antiviral drugs that could be repurposed and administered via the pulmonary route to treat COVID-19 and other respiratory infections.

Many studies are ongoing to develop antiviral, anti-inflammatory drugs as formulations suitable for inhalation. Some of these studies are under clinical trials (Phase 1 or Phase 2) for the management of COVID-19. Some of these studies are in table 1. The following sections will focus in some detail on antivirals.

3.1.1 Inhaled Hydroxychloroquine

Currently, there are inhalable HCQ formulations under investigation. In 2005, Aradigm//apt Pharmaceuticals developed a nebulized HCQ formulation [49,73].
Table 1. Ongoing studies of lung delivery of medications against COVID-19

<table>
<thead>
<tr>
<th></th>
<th>Status                                                                +-+-+-+-+-+-+-+-+-+-+-+-+-+-+</th>
<th>Ref</th>
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</thead>
<tbody>
<tr>
<td><strong>Antiviral</strong></td>
<td></td>
<td></td>
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<tr>
<td>HCQ</td>
<td>Formulation: dry powder</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>formulation, Liposomal, PK</td>
<td>[47]</td>
</tr>
<tr>
<td></td>
<td>Nanocarrier</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>Hypothesis</td>
<td>[49]</td>
</tr>
<tr>
<td>Azithromycin (AZ)</td>
<td>Discussion of the rationale of the repositioning of azithromycin and ambroxol, with the advantageous use of inhaler drug delivery</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>Formulation and evaluation of nebulized nanovesicle formulation, nanoarchaeosome-AZ (nano ARC-AZ). Ex vivo- enhanced antimicrobial activity.</td>
<td>[51]</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>Formulation. Dry powder Thin-film freezing</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td>PK of dry powder inhalation in an animal model</td>
<td>[53]</td>
</tr>
<tr>
<td></td>
<td>Suggested Nanospry formulation using poly (lactic-co-glycolic) acid</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td>Formulation. Nano liposomal carrier</td>
<td>[55]</td>
</tr>
<tr>
<td>Niclosamide</td>
<td>Formulation of dry powder by thin-film freezing (TFF) and evaluation of PK &amp; safety in rats and hamsters</td>
<td>[56]</td>
</tr>
<tr>
<td></td>
<td>Phase 1 trial to -assess the safety of UNI91104 (concentrated solution of niclosamide for inhalation and intranasal application)</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td>in healthy volunteers. Formulations are Well tolerated with transient irritation only after inhalation</td>
<td></td>
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<tr>
<td></td>
<td>Formulation and evaluation of composite niclosamide-lysozyme particles for lung delivery</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td>Formulation and characterization of combination formulations of colistin and azithromycin for lung delivery</td>
<td>[59]</td>
</tr>
<tr>
<td><strong>Antiviral</strong></td>
<td>lyophilized ivermectin-cyclodextrin formulation, good Safety for pulmonary ivermectin administration in rats in doses of 0.05 and 0.1 mg/kg in rats.</td>
<td>[60]</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>ethanol-based ivermectin formulation, PK and safety study in rats, effective concentration was achieved in lung tissues, no histological changes</td>
<td>[61]</td>
</tr>
<tr>
<td></td>
<td>PK and safety of Nasal Spray Formulation (Pig Model).</td>
<td>[62]</td>
</tr>
<tr>
<td></td>
<td>Achievement of adequate drug level nasopharyngeal and lung tissues. No local/systemic adverse events were observed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothesis discussing limitations of an oral formulation, the rationale of inhalation of the drug, addressing its antiviral and anti-inflammatory effect</td>
<td></td>
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<tr>
<td><strong>Immunomodulators</strong></td>
<td></td>
<td></td>
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<tr>
<td>Nezulcitinib</td>
<td>Phase 1 clinical trials, safety and PK in healthy volunteers. Promising results</td>
<td>[64]</td>
</tr>
<tr>
<td></td>
<td>A phase 2 multiple ascending dose studies of the inhaled is severe COVID-19 patients. Showed promising additive anti-inflammatory effect</td>
<td>[65]</td>
</tr>
<tr>
<td>Interferon -γ-</td>
<td>Preclinical studies in an animal model</td>
<td>[66]</td>
</tr>
<tr>
<td>Interferon-alpha-2b</td>
<td>Clinical trial in COVID-19 patients, improve clinical outcome</td>
<td>[67]</td>
</tr>
<tr>
<td>IFN-κ &amp; Trefoil factor 2 and TFF2,</td>
<td>Pilot clinical trial in COVID-19 patients</td>
<td>[68]</td>
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<tr>
<td><strong>Natural compounds</strong></td>
<td></td>
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<tr>
<td>Resveratrol</td>
<td>Formulation and evaluation of spray-dried formulation</td>
<td>[69]</td>
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<tr>
<td></td>
<td>Co-spray dried formulation with budesonide</td>
<td>[70]</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
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<tr>
<td>Heparin</td>
<td>The hypothesis to the pharmacological bases and advantages of inhaled heparin in the management of COVID-19</td>
<td>[71]</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Clinical trial in hospitalized COVID-19 patients, results suggest it likely to be safe and modulates the immune system</td>
<td>[72]</td>
</tr>
</tbody>
</table>
Table 2. A summary of promising inhaled formulations of antiviral drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Current Route</th>
<th>Limitation of the current route</th>
<th>Potential advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niclosamide</td>
<td>oral</td>
<td>Poorly water-soluble, oral absorption is limited, inadequate concentration in lung tissues</td>
<td>Higher efficacy, lower toxicity</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>IV</td>
<td>Not appropriate for outpatients, limited efficacy in severe cases, adverse effects</td>
<td>Higher efficacy, lower toxicity, use in outpatients</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>oral</td>
<td>Variably pharmacokinetic. Very slow onset, cardiac toxicity</td>
<td>Higher efficacy, lower toxicity</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Oral and IV</td>
<td>Potential cardiac toxicity, low efficacy</td>
<td>Higher efficacy, and lower toxicity. Synergistic effect</td>
</tr>
</tbody>
</table>

PureIMs partnered with the University of Groningen and global collaborators for the first human trial of dry powdered HCQ in the PureIMs Cyclops™ inhaler. The calculated dosage to attain high local concentrations in patients’ airways was about 20 mg [74]. TLC has currently started to evaluate inhaled HCQ as liposomal formulation (TLC19) in phase 1 administered using a mesh nebulizer [75].

3.1.2 Inhaled azithromycin

Azithromycin (AZ) is a broad-spectrum antibiotic suggested recently to have a potential role in the management of COVID-19 with its anti-inflammatory and antiviral activities. However, oral or parenteral use is associated with many adverse effects including cardiac toxicity [76-78].

Debates exist regarding its efficacy in the management of COVID-19 and there are concerns of its serious potentiation of cardiac toxicity of other medications as HCQ. Thus, further research of an inhalable formulation of AZ was suggested.

Double emulsion/solvent evaporation technique was used to formulate AZ as polycaprolactone microparticles. These low-density AZ loaded microparticles showed good characteristics that can aid local treatment of pulmonary infections [79].

A study involved Acorn II, Updraft, and LC Plus nebulizers, operating at 8 L/min, delivering three AZ different concentrations (10, 50 and 100 mg/mL). It demonstrates that the dose administered to the lung is maximal when using the LC Plus nebulizer and achieved the highest dose concentration of AZ [80].

Andisheh et al. assessed the short-term efficiency and protection afforded by nebulized AZ as an anti-inflammatory treatment. Their research involved cystic fibrosis patients aged (8-18 y), and suffered chronic infection of pseudomonas aeruginosa. They demonstrated that nebulized AZ provided better efficacy and safety profile [81].

AZ was loaded within N-fumaroylated diketopiperazine microparticles to provide effective pulmonary delivery. In vitro and in vivo results indicated that these formulations delivered by the intratracheal insufflation method resulted in an effective local therapeutic concentration with good retention time and minimum systemic exposure. The lung tissue concentration with this formulation was four times higher than that after administration of equivalent dose either IV or orally [82].

3.1.3 Inhaled remdesivir

According to Gilead Sciences, early use of inhaled RDV is likely to be more efficient than IV routes and potentially reduces any adverse side effects. The nebulizer’s ability to directly deliver remdesivir via inhalation to the primary infection site could prove especially useful because it allows achievement of therapeutic concentration at the lung tissues and can be administered to outpatients. Additionally, it reduces the incidence of systemic side effects associated with IV administration. The inhaled formulation is currently undergoing a phase I assessment comprising 60 healthy adults [83,84].

Austin-based University of Texas successfully formulated the drug as a dry powder ready for inhalation and employs the thin film freezing (TFF) technique to develop a highly potent inhalable RDV [52].

3.1.4 Inhaled niclosamide

Niclosamide (NIC), an anthelmintic drug, has been repositioned to treat lung diseases, such as...
cystic fibrosis and asthma. The drug inhibits the production of mucus and has a marked bronchodilator effect as well as an antibacterial activity, which suggest its utility for the management of respiratory tract infections [85,86]. Also, NIC affects intracellular Ca^{2+} concentration and suppresses the release of proinflammatory cytokines, such as IL-8. These characteristics represent the rationale for its role in ameliorating COVID-19 induced cytokine storm [85,87].

Research has found that NIC suppresses the reproduction of Middle East respiratory syndrome coronavirus (MERS-CoV) and recent research documented its activity against SARS-CoV-2. The drug’s antiviral effects include suppressing the viral replication through inhibiting S-phase kinase-related protein 2 (SKP2) [85,87].

However, NIC demonstrates poor bioavailability. Therefore, adequate therapeutic antiviral level was postulated not likely to be attained with oral formulations [85,88-90].

At the University of Texas, Austin, efforts have been made to formulate NIC inhalation with human lysozyme (hLYS), an abundant endogenous protein found in the upper and lower respiratory tracts. These formulations showed promising results in both in vitro studies and animal models [91].

The same institute also developed and assessed dry powdered NIC using the TFF technique that was administered via inhalation to an animal model with focusing on its toxicology and PK properties. This approach led to the development of an inhalable NIC powder composition with an admissible aerosol performance [56]. Three-day multi-dose tolerability and exposure involving rats and a histopathological assessment revealed that the resultant substance was safe and usable, and could achieve lung concentrations that exceeded the necessary IC_{90} levels for at least a single day following its administration [56].

Such developments indicate NIC’s viability as an inhalable medication overcoming its limited oral bioavailability by ensuring its direct administration to the primary COVID-19 infection area.

4. CONCLUSION

A summary of promising inhaled formulations of antiviral drugs is presented in table 2. Since the respiratory tract is a primary site of coronavirus infections associated with COVID-19, pulmonary drug delivery offers reassuring evidence that repurposing drugs and administering them through such a route can be an effective method of treating respiratory diseases. Despite such findings, there is still only a limited number of pulmonary formulations under investigation. Thorough evaluations have not been carried out on all repurposed drugs to explore their feasibility for pulmonary delivery. These evaluations must include histopathology screening to demonstrate their safety. Pulmonary delivery is a very promising approach to overcome limitations of antiviral medications against COVID-19, and likely offer enhanced efficacy and minimal toxicity.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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