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# THE COVID-19 PANDEMIC AND THE USE OF PHARMACEUTICAL NANOTECHNOLOGY

**Mahamuda Fatema, Nafisah Mahjabin*, Susmita Roy Ria, Furhatun-Noor, Md. Asadujjaman, Mohammad Taleb Hossain and Md. Harun Ar Rashid**

Department of Pharmacy, Faculty of Health Science, Northern University Bangladesh, Dhaka-1230, Bangladesh.

***Corresponding Author: Nafisah Mahjabin**

Department of Pharmacy, Faculty of Health Science, Northern University Bangladesh, Dhaka-1230, Bangladesh.

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## ABSTRACT

As of right now, there is no effective treatment for COVID-19. Many medications that have been studied in recently as possible COVID-19 therapies have shown considerable toxicity and poor efficacy. Consequently, loaded medications can have their therapeutic effect enhanced and their toxicity reduced by the application of nanotechnology. We outlined the medications investigated as COVID-19 treatments in this review, along with the benefits of viral nanostructured drug delivery systems. Compared to free medicines, these systems have shown lower toxicity and improved antiviral efficacy. We think that in order to find effective COVID-19 therapies, this strategy should spur the development of innovative nanostructured drug delivery methods. Here we address the remaining obstacles in the way of approving such promising nano systems for therapeutic application.

**KEYWORDS:** COVID-19, virus, nanotechnology, toxicity, therapy, pandemic etc.

## INTRODUCTION

A significant worldwide scenario pertaining to the SARS-CoV-2 virus, which causes COVID-19, has been observed in 2020.[1] On December 31, 2019, in Wuhan, China, the first data was recorded. In a few of months, it quickly swept throughout China before going global.[2] The global health and economic crises are caused by changes in human behavior brought on by this coronavirus-based infection, which produces a variety of symptoms, including pneumonia and infected patients' deaths.[3] Since there is currently no vaccination or efficient treatment for COVID-19, the situation is always changing. In order to help put an end to the COVID- 19 epidemic, experts have moved efforts to produce safe and effective vaccinations, therapies, and diagnostic technologies.[4] Certain medications, involving chloroquine or hydroxychloroquine, have gained popularity as therapeutic candidates.[5] Tests have been conducted on additional antivirals and antibiotics against COVID- 19 (Table 1). Regretfully, it has become apparent that the suggested therapies have a high level of toxicity and low bioavailability. So Pharmacological treatment for COVID- 19 remains difficult. Pharmaceutical formulations with the ability to encapsulate, incorporate, intercalate, or adsorb various active compounds are known as nanostructured drug delivery systems, or NDDS. To interact with the target cells, the composition, pH, surface charge, and nanoparticle size distribution should all be molecularly planned.[6] NDDS are frequently made up of various biomaterials and processed into a variety of pharmacological forms for use in a variety of applications.[7] The goal of antiviral NDDS is to lessen drug toxicity without sacrificing its effectiveness. The longer release profile of the entrapped pharmaceuticals makes it possible to enhance the therapeutic impact even at lower drug concentrations.[8] Many antiviral based NDDS, primarily made of lipids, polymers, metals, and inorganic nanoparticles, have been reported in recent years as treatments for various viral diseases, including HIV, herpes zoster, and viral C hepatitis.[3] These lipids or polymer-based systems, or their combinations, merit consideration due to their low cost, biocompatibility, biodegradability, and large-scale repeatability[9], as well as their promisor nanocarriers properties. Generally, RNA polymerase, viral protease, and viral S protein interaction can all be targets of NDDS. IFN-γ-inducible protein 10 (IP-10), surface S protein, IL 6, and the viral RNA genome can all be targeted by NDDS against SARS-CoV-2. We think that in order to find effective COVID-19 therapies, this strategy should spur the development of innovative nanostructured drug delivery methods. Here we also address the remaining obstacles in the way of approving such promising nano systems for therapeutic application.

**Table 1: Drug candidates evaluated in terms of drugs, target binding, assay type, and conventional uses against different types of viral complication.**

| Drug | Target | Assays | Usual treatment |
|---|---|---|---|
| Galidesivir | Bind RdRp | In silico | Hepatitis C virus (HCV) |
| Arbidol | Binds to hemagglutinin | In vitro | Influenza, arboviruses |
| Dactinomycin† | RNA synthesis inhibitor | In silico | Cancer |
| Atazanavir | Inhibition of the 3CLPRO | In silico, in vitro | HIV |
| Emetine | Inhibits the replication of RNA viruses | In vitro | Amoebiasis |
| Chloroquine | Immunomodulatory effects, increase endosomal pH required for virus | In vitro, clinical trial | Malaria |
| Darunavir | Protease inhibitor | In silico | HIV |
| Dolutegravir | Protease inhibitor | In silico | HIV |
| Efavirenz | Inhibition of the 3CLPRO | In silico | HIV |
| Emodin | Blocked the interaction between the spike and ACE2 | In silico, in vitro | Cancer |
| Mercaptopurine | Inhibition papain-like protease | In silico, in vitro | Cancer and auto-immune diseases |
| Favipiravir | RNA-dependent RNA polymerase (RdRp) inhibitor | In vitro, clinical trial | Influenza |
| Sofosbuvir | Bind RdRp | In silico | HCV |
| Hydroxychloroquine | Immunomodulatory effects, increase endosomal pH required for virus | In vitro, clinical trial | Malaria |
| Tenofovir | Bind RdRp | In silico | HIV |
| Ivermectin | | In vitro | Parasites |
| Lopinavir-ritonavir | inhibition of the 3CLPRO | In vitro, clinical trial | HIV |
| Melatonin‡ | regulates ACE2 expression | In silico | Several including insomnia |
| Remdesivir | Inhibition the RdRp/Seems to inhibit of the 3CLPRO | In silico, in vitro, in vivo | HIV/Ebola |
| Ribavirin | Inhibits RdRp | In silico | HCV, respiratory syncytial virus (RSV) |
| Saquinavir | inhibition of the 3CLPRO | In silico | HIV |
| Sirolimus† | Inhibitor of mTOR | In silico | Antifungal and cancer |
| Tirolone | Inducer of interferon | In vitro | Influenza, hepatitis, viral encephalitis and others |
| Toremifene | Destabilizing the virus membrane glycoprotein | In silico, in vitro | Cancer |

These systems can be effectively utilized as smart delivery systems by active molecules such as RNase, which effectively inhibit viral replication.[10] Antiviral delivery to the target is improved by positively charged nanocarriers that enable electrostatic interaction with anionic viral envelopes, such as DOTAP-based liposomes. Formulations based on phospholipids have a role in viral entry and show promise as antiviral nanocarriers.[11] However, it has been demonstrated that some biopolymers, like carrageenan and chitosan, have significant inherent antiviral qualities. Furthermore, the virus entry process can be altered by NDDS-based carbohydrate-binding agents, such as sulfated polymers, which block the viral cationic surface receptors and prevent the virus from interacting with the host cell surface's heparan sulfate proteoglycan.[12] But still NDDS has not yet been reported as a COVID-19 treatment. Notwithstanding these compelling benefits over conventional medication treatments, nanomaterials remain unregulated, delaying the approval process for applications and clinical trials. This review provided an overview of pertinent data pertaining to general coronavirus properties that are associated with the primary treatment candidates under investigation. In order to spur new discoveries, we therefore clarified the most NDDS for antiviral applications described.

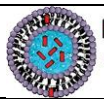
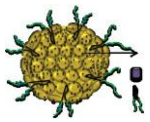
Additionally, we have offered an important viewpoint on this current scenario, emphasizing the necessity of government and multidisciplinary initiatives to support the creation and approval of nanostructured formulations.

**General characteristics of coronavirus**

The positive stranded RNA that is enveloped is present in members of the family Coronaviridae. The large RNA that encodes nonstructural proteins like RNA-dependent RNA polymerase (RdRp), papain-like protease, chymotrypsin like, RNA helicase encoded by the replicase, other accessory and regulatory proteins, and structural proteins is present in spherical, 120 to160 nm virions. The main factor inducing antibodies that neutralize viruses is the S protein. Furthermore, the high degree of variability observed in the S and hemagglutinin (HE) proteins points to significant antigenic drift and shifts. Because coronaviruses can mutate and recombinate to adapt to new environments or hosts, they can effectively change tissue tropism and host range.[13] Prior to the discovery of SARS CoV in 2002, coronaviruses only produced minor symptoms in people[14] In 2012, MERS-CoV was another disease that killed a significant number of people in humans. SARS-CoV-2, formerly known as 2019-nCov, was initially isolated in 2019.[15] The World Health Organization classified the SARS-CoV-2-caused illness known as COVID-19, which spread quickly and was extremely contagious.[16] This caused changes in human behavior that had an effect on the world economy and health. Humans and other mammals become ill due to the Alphacoronavirus and Betacoronavirus.[17] Alphacoronavirus and betacoronavirus can be pathogenic in domestic and livestock mammals.[18] While SARS-CoV, SARS-CoV-2, and MERS-CoV, viruses from the Betacoronavirus lineage B, cause severe respiratory syndrome in humans, other human coronaviruses, like HCoV-OC43, HCovKU1, HCoV-NL63, and HCoV-229E, may only cause mild symptoms, with the exception of severe infections in young children, the elderly, or immunocompetent patients.[19] It appears that rodents are the source of the Betacoronavirus lineage A.[20] However, it is possible that bats are the source of HCoV-NL63 and HCoV-229E (Alphacoronavirus).[21] According to certain earlier research, the coronavirus that caused SARS-CoV was most likely spread by bat species from wildlife markets in China to other mammals, such as masked-palm civets, raccoon dogs, and ferret-badgers[22] Bats were most likely the source of the novel human pandemic virus in COVID-19. Even though the epidemiology is still not fully understood, animals like Manis javanica, or Malayan pangolins, may also be involved.[23]

**Principal medication candidates for treating COVID-19**

There is currently no effective anti-COVID-19 medication on the market, despite the existence of several promising candidates for COVID-19 treatment. Furthermore, the majority of the reports only included information on in vitro and in silico tests. Numerous medications that inhibit viruses or cells have been researched, in addition to immunomodulators, peptides, vitamins, and antibodies. The primary medications evaluated against MERS, SARS-CoV, and SARS-CoV-2 that may be suitable options for the treatment of COVID-19 (Tabl- 1). The majority of potential medications for treating SARS-CoV-2 generally displayed high toxicity. In addition to cardiovascular and cerebrovascular effects, many protease inhibitors cause dyslipidemia, insulin resistance, and lipodystrophy/lipoatrophy as side effects.[24] Drugs such as chloroquine and hydroxychloroquine have been known to cause cardiac rhythm abnormalities, and they should not be administered to patients who have liver or renal impairments.[25] Some of the individuals at risk of the current pandemic are elderly and patients with chronic illnesses, who are severely impacted by these side effects.[26] Table-1 showed that while numerous drugs were tested for treating COVID-19, very few clinical trials were carried out, and opinions on the drugs' efficacy were divided. The drug concentration that works best against COVID-19 cells is typically very cytotoxic. The primary drawbacks of the suggested treatments are their high toxicity and low efficaciousness.

| Nanocarriers | Main composition | Size (In nm) | Loaded molecules | IIIustrative scheme |
|---|---|---|---|---|
| **Cyclodextrins** | Cyclic oligosaccharides | 5–50 | Hydrophilic, hydrophobic |  **Drug** |
| **Dendrimers** | Oligosaccharides | 3–20 | Hydrophilic, hydrophobic |  **Drug** **Initiator core** |
| **Liposomes** | Phospholipids | 50–900 | Hydrophilic, hydrophobic |  **Drug** **Amphiphilic lipid** |
| **Nanostructured lipid carriers** | Solid and liquid lipids, surfactant | 100–500 | Hydrophobic |  **liquid lipids** **Drug** **Surfactant** |
| **Nanoemulsions** | Liquid lipid, co- | | | |

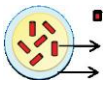
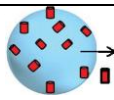
| | | | | |
|---|---|---|---|---|
| | surfactant, surfactant | 20–200 | Hydrophilic, hydrophobic |  **Drug** **Oil phase** **Water phase** |
| **Solid lipid nanoparticles** | Solid lipid, surfactant | 100–500 | Hydrophobic | **Solid lipid Drug Surfactant** |
| **Polymer nanoparticles** | Polymer, crosslinking agent | 100–900 | Hydrophilic |  **Drug** |

**Figure 1: An illustrative chart that shows the composition, size range (in nm) of reported soft nanostructured drug-delivery systems with antiviral properties, as well as their capacity to load molecules and schematic representation.**

**Drug delivery systems with nanostructures**

Paul Ehrlich (1854 to 1915) published a description of the first drug delivery system (DDS), known as "The Magic Bullet," in 1909. He used the idea of drug release at a specific target as the foundation for his investigation. This arsenic based contraption included a novel syphilis treatment, which was the most effective anti-syphilitic medication available until the discovery of penicillin in 1940. Since then, the field of multidisciplinary DDS has expanded rapidly, particularly for those with nanotechnology-based designs.[27] Many medications and natural compounds can be encapsulated, intercalated, adsorbed, or incorporated using NDDS, which can be made of inorganic, organic, or hybrid biomaterials.[28] The main objectives of NDDS are to increase the effectiveness of loaded active molecules and lengthen their release profile through the use of lower doses, which minimizes systemic side effects due to the optimal interaction with the biological barriers of interest.[7] In order to capitalize on a number of characteristics, including their capacity to pass through biological barriers, surface functionalization to improve bioavailability, and biomimetic structure to boost specificity and lower antiviral resistance, these systems are designed with varying compositions and morphologies.[4] The most highly active NDDS reported are soft-based NDDS made of polymers as nanoparticles, cyclodextrins (CD), and dendrimers and lipids as liposomes, solid lipid nanoparticles, nanostructured lipid carriers (NLC), and nanoemulsions (Fig. 1). We therefore concentrated on these developments in the current review. Formulations against HIV are highly noticeable among the suggested treatments.[28] The persistence of HIV infection in humans is caused by cellular and anatomical viral reservoirs. Scientists have therefore shifted their efforts to prevent HIV replication. When patient adherence is greater than 95%, traditional medication therapy for symptom management is successful; when it is less than this, 50% of treatment failures occur. Due to the unfavorable side effects, it is also necessary to administer a drug cocktail at high concentrations throughout life, which significantly reduces patient compliance to the treatments. In this regard, solid lipid nanoparticles (SLN) (made of stearic acid and poloxamer 188) loaded atazanavir (200 nM), an HIV protease inhibitor, to improve the antiretroviral brain delivery. The blood–brain barrier was simulated using a human brain micro vessel endothelial cell line. Compared to the free drug, SLN, which has a particle size of about 170 nm, allowed for greater drug cellular accumulation without exhibiting any in vitro toxicity. Antiretroviral medication resistance and HIV encephalitis were prevented by this formulation.[29] Another study described the use of immunoliposomes to encapsulate HIV-infected cells that target N-butyldeoxynojirimycin. This molecule inhibits the folding of HIV gp120 and is currently used to stop the spread of HIV/AIDS. The antiviral activity was tested in It was observed that HIV-nfected cells treated with lower doses of NB-DNJ liposomes reduced by about 80–95%. In an effort to create a less hazardous anti-HIV treatment, Clayton and colleagues (2009) also suggested the use of immunoliposomes for the targeted delivery of HIV-1 protease inhibitor (PI1). HIV-gp120-directed monoclonal antibody F105-targeting ligand, which is derived from HIV-gp120-directed monoclonal antibody F105, was used to coat PEGylated liposomes. Immunoliposomes showed that HIV-1-infected cells with an intracellular location would selectively absorb them, creating a PI1 reservoir. Furthermore, the formulation was found to have greater antiviral activity when compared to conventional liposomes or free drug.[30] There have also been reports of anti-HIV medication delivery using polymer nanocarriers. Recently, lopinavir (a protease inhibitor) was loaded onto CD, which is composed of cross-linking pyromellitic dianhydride (PMDA) with two CD derivatives (methyl-β-CD-MβCD and (2-hydroxy)propyl-β-CD-HPβCD). About a 13-fold increase in antiviral solubility was caused by the complex. According to an in vitro infectivity test, the complex antiviral-CD exhibited a maximum percentage inhibition of HIV-1 cells ranging from 79 to 91%. This indicates that the antiviral activity is excellent against HIV without compromising its safety. In other research, elvitegravir was loaded into poly (lactic-co-glycolic acid) (PLGA) nanoparticles to improve viral suppression in HIV-infected macrophages. When compared to free drug, the CD was created by loading lopinavir (a protease inhibitor) onto pyromellitic dianhydride (PMDA) and cross-linking it with two CD derivatives (methyl-β-CD-MβCD and 2-hydroxy) propyl-β-CD-HPβCD). About a 13-fold increase in antiviral solubility

was caused by the complex. According to an in vitro infectivity test, the complex antiviral-CD exhibited a maximum percentage inhibition of HIV-1 cells ranging from 79 to 91%. This indicates that the antiviral activity is excellent against HIV without compromising its safety. In other research, elvitegravir was loaded into poly (lactic-co-glycolic acid) (PLGA) nanoparticles to improve viral suppression in HIV-infected macrophages. When compared to free drug, the formulation had greater penetration and intracellular uptake of HIV-1-infected human monocyte-derived antiviral delivery was extended for 50 hours using the mouse fibroblast cell line (L929). Additionally, this formulation prevented side effects and the drug's degradation in the simulated gastric medium.[31] Promising therapies for various viral illnesses have also been effectively developed and made available. To increase acyclovir's penetration through the stratum corneum, a chitosan-based NE was created. According to an in vitro permeation test, NE with particles sized approximately 200 nm was able to cross the porcine skin barrier more effectively than free drug. Confocal laser scanning microscopy was used to confirm the increased anti-herpes zoster activity, which was observed with higher uptake of HSV-1 and HSV-2 infected cells than control. Conversely, the hepatitis C virus (HCV) is a significant RNA virus that impairs human quality of life. Thus, apolipoprotein A-I, which loads onto cationic liposomes, was created as a liver-target siRNA. Following liposomal intravenous administration, the formulations' capacity to suppress the expression of HCV proteins in mouse hepatocytes was assessed. A single 2 mg siRNA/kg dose prevented 65–75% of viral gene expression in mouse liver during the first two days of treatment without causing any immunotoxicity. Furthermore, for nearly a week, the gene-silencing effect was observed.[32] An ophthalmic formulation for treating ocular HSV and cytomegalovirus (CMV) infections was described by Shen and colleagues. Transcorneal permeation, clearance, and pharmacokinetic profile of liposome-loaded ganciclovir (GCV) with approximately 51% encapsulation efficiency were assessed in rabbits. Liposomes were found to have a higher capacity for liposomes had a nearly two-fold higher curve than free drug, and their distribution and bioavailability in ocular tissue were better. It has been repeatedly shown recently that viruses affecting the upper respiratory tract can cause severe symptoms, including fatalities. As recently described by Al-Halifa and colleagues, nanotechnology is an emerging tool used to increase the effectiveness of conventional antiviral therapy and to provide vaccines against respiratory viruses. Up until recently, influenza virus infections were thought to be the main global public health concern. months prior. Targeting viral proteins served as the foundation for most treatments. Drug resistance is currently caused by viral variants, though. This has made it possible to design antivirals that target pathogens, like the viral target vacuolar ATPase, which blocks the entry of influenza viruses into host cells.[33] PEG-PLGA nanoparticles (~200 nm) with an encapsulation efficiency of 42 and 100%, respectively, were synthesized for the sustained release of bafilomycin and diphyllin for the treatment of influenza. The antiviral drugs were released over a 72-hour period by the systems, exhibiting reduced cytotoxicity and increased intracellular uptake in comparison to free drugs. The administration of polymer nanoparticles to mice exposed to both lethal and sub-lethal influenza challenges Moreover, it received a survival index that was 30% greater than the control group. A different study has suggested a treatment for the influenza A virus that involves blocking viral attachment and cell entry by synthesizing 6SL-PAMAM (6r-sialyllactose-polyamidoamine) dendrimer conjugates. Without significantly causing weight loss (a toxicity indicator) in mice infected with influenza A, these dendrimer-based formulations preserved approximately 75% of the mice in the lethal challenge test, inhibiting lung infection in mice nearly tenfold more than the control group. As COVID-19 therapy, it is noteworthy to mention that advancements in antiviral-based NDDS made of inorganic matrices are also worthy of consideration. More recently, Palmieri and Pap have given comprehensive details about graphene's potential use as a COVID-19 treatment. The majority of efforts have been focused on creating sensors and diagnostic tools based on graphene. However, in addition to graphene's inherent antiviral properties, its bidimensional sheet-like structure can be functionalized by antibodies that target viral proteins, making it a promising matrix for drug/gene delivery for the treatment of COVID-19.[34] Conversely, research has been done on the antiviral activity of silver nanoparticles (SN) against a number of viruses, including respiratory syncytial virus, HSV, and HIV. Baram- prevention of viral penetration in vitro. In cell culture, SN demonstrated the ability to prevent HSV-1 infection and biocompatibility. Furthermore, because titanium dioxide nanoparticles (TiO2) can specifically target the viral host cell by damaging the lipid viral envelope, they have also been studied as antiviral agents. By immobilizing DNA fragments to TiO2, Levina and colleagues were able to create a nanocomposite that exhibited antiviral activity against the influenza A virus. With the help of this system, nucleic acids could be efficiently delivered into the cells without the need for transfection agents. As mentioned above, despite all the advancements in antiviral-based NDDS, no particular and efficient treatment for COVID-19 has been described as of yet. There are just two reports of NDDS being used to treat diseases related to the Coronaviridae family. Targeting a conserved region of viral RNA, a pharmaceutical hybrid composition consisting of functionalized spermine-liposomes (100–400 nm) based on polymer technology was patented last year for pulmonary delivery of siRNA. Infected VERO cells were the target of the intranasal formulation's selective release of siRNA, which also prevented the expression of the MERS-CoV gene in mice in vivo.[35] A fatal and incurable viral infection in cats, feline infectious peritonitis (FIP) is another disease caused by the

Coronaviridae family. Consequently, Hu and associates offered There are just two reports of NDDS being used to treat diseases related to the Coronaviridae family. Targeting a conserved region of viral RNA, a pharmaceutical hybrid composition consisting of functionalized spermine-liposomes (100–400 nm) based on polymer technology was patented last year for pulmonary delivery of siRNA. Infected VERO cells were the target of the intranasal formulation's selective release of siRNA, which also prevented the expression of the MERS-CoV gene in mice in vivo. A fatal and incurable viral infection in cats, feline infectious peritonitis (FIP) is another disease caused by the Coronaviridae family. Consequently, Hu and associates offered formulations that use diphyllin-encapsulated PEG-PGLA nanoparticles (~40 nm) to function as a viral V-ATPase inhibitor. After giving a high dose intravenously to mice that were 8 weeks old, the authors showed that this system was biocompatible by reducing the replication of FIP. Polymer nanoparticles showed a stronger antiviral effect against FIP than free drug in the in vitro model of antibody-dependent enhancement of FIP infection.[36]

## CONCLUSION

The world is a living example of the COVID-19 pandemic's effects on health and the world economy. Researchers from all around the world are working hard to realize the unique characteristics of this viral infection and the dynamics of the pandemic, in the still-challenging goal of creating safe and effective treatment. A promising method for increasing medication efficacy without sacrificing drug safety is nanotechnology. There have been reports of various NDDS with antiviral properties. It was shown to have a number of benefits over conventional therapies. Lastly, in order to transcend the scholarly divide, additional R&D study and funding and targeted legislation are desperately needed so that NDDS can be used as COVID-19 treatments that work.

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