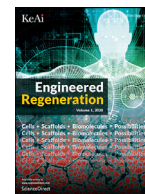




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Nanoparticles as delivery vehicles for antiviral therapeutic drugs

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ABSTRACT

With the ongoing COVID-19 pandemic still escalating, many researchers are turning to nanotechnology as a method of treatment not only for this pandemic, but in preparation for the pandemics of the future. Given both a wide variety of biomaterials at their disposal and the recent rise of nanotechnology, scientists now have the means to release and distribute therapeutic drugs in a variety of ways. Such a variety permits medical professionals the ability to choose biomaterials and methods that would provide the best release and treatment methodologies for the viral ailment they are attempting to remedy. This integrative review discusses context of previous pandemics, viral pathogenesis, issues associated with the current state of antiviral delivery systems, numerous biomaterials used for this purpose, and further information regarding the ongoing global COVID-19 pandemic.

1. Introduction

Just over 100 years ago the 1918 Spanish Influenza pandemic plagued the world. A viral strain of the H1N1 influenza A virus caused the flu. The virus infected close to $\frac{1}{3}$ of the world's population and caused the death of between 50 and 100 million people. This outbreak spurred scientific research into antiviral treatment and vaccination against the virus. It would not be until 1945 when the first inactivated influenza vaccine was made available in the U.S. for civilians [4]. Despite the vaccine, there have been several other influenza pandemics including in 1957 (H2N2), 1968 (H3N2), and 2009 (H1N1pdm). All three outbreaks derived themselves from the original 1918 H1N1's genetic code. These additional strains represent the danger of viruses and show why antiviral treatment is so difficult [5].

The influenza virus is not the only one that has posed a significant threat to human life over the past century. The HIV epidemic began in the early 1980's, but it was not until it had infected millions of people in 1996 that an antiretroviral treatment became the standard. HIV/AIDS is still a death sentence for most people. The complex antiviral drug cocktails given to carriers only slow and prolong the process [6]. Besides HIV, outbreaks of viruses such as HPV, HCV, HBV, Dengue and Ebola have all had negative effects on global health. The death rates and spread being far greater in less economically prosperous regions.

In present times, the coronavirus has affected life on six of the seven continents. Economies have shuttered, and resources have been stretched thin. COVID-19 has killed nearly 2.35 million worldwide, and it has infected 50 million [7]. Even the most advanced of nations will remain in limbo, as economic and social damage mounts until an effective antiviral therapy or vaccine is developed and made available.

The clock on science is ticking. Viruses, it is clear, are here to stay. They will continue to pose a threat to global public health as long as there are human or animal hosts whose cells they can use to replicate. For the good of civilization, the world's eyes must turn to every possibility for antivirals.

One facet of antivirals being explored with great intrigue, is the drug delivery mechanism, particularly nanoparticulate based delivery systems. At present, many pharmaceutical companies are experimenting by altering their existing antiviral drugs mechanisms to fall on the nanoscale or to be delivered via nano scaled vehicles. Such experiments have shown promising results, with the antiviral delivery by nanoparticle considered more effective than by traditional mechanisms, and the advantages of this means will be discussed to a great extent throughout this paper. Furthermore, it is important to note that these nanoparticles are not new molecules, but rather smaller versions of existing drug delivery capsules such as liposomes, emulsions, and polymers. Therefore, in order to most effectively solve the virus-related global issues, science should place its focus on nanoparticles as antiviral drug delivery systems.

Overall, throughout this paper, we will discuss several prevalent forms of nanoparticles that have shown great promise for antiviral drug delivery. This includes material-based nanoparticles like carbon-based and cyclodextrin based molecules; cell structure mimics, such as micelles and exosomes; lipid and polymer based including liposomes, solid lipid nanoparticles, polypeptides and dendrimers; nanoscaled materials such as nanoemulsions, nanogels and nanocrystals; metal-based nanoparticles including metal organic frameworks; nanovaccines; and future nanosystems such as nanorobots. Although this is quite a large list

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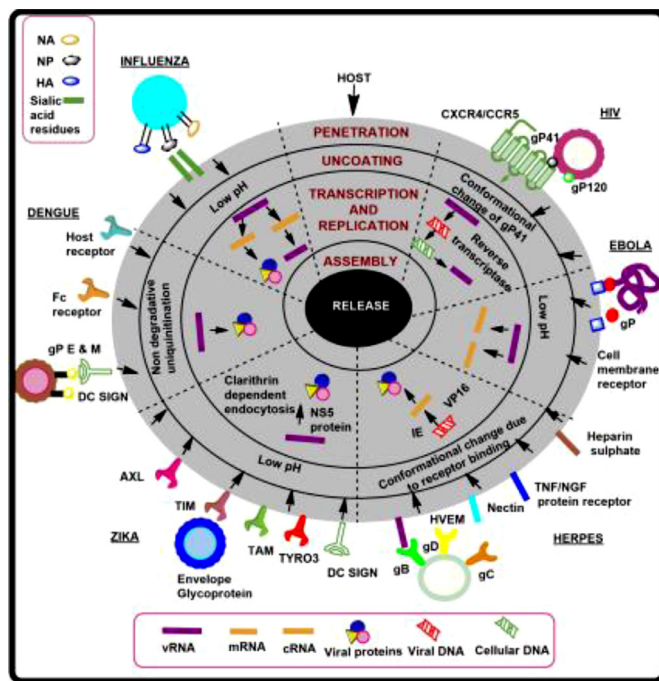


Fig. 1. Illustration of the six major steps of pathogenesis for common viruses.[1].

of materials, it is imperative to note that the materials discussed in this paper are not exhaustive. Furthermore, in addition to relevant information regarding each type, potential nano-applications will be discussed for their potential utility in treating SARS-CoV-2. Overall, the nanoparticle realm of science is already vast, but will continue to expand in both number of structures, as well as its uses in the future. With that fact in consideration, this paper should act as a review of current materials and their respective relevant clinical uses for viral infections.

2. Viral pathogenesis

Viruses are incredibly difficult to treat for a multitude of reasons. However, it is the way they spread that poses the initial threat. Not every person infected with a virus will show symptoms. In fact, as with COVID-19, most of those infected will present as subclinical. This means that the infected person shows few to no symptoms of infection and is therefore unlikely to ever be diagnosed. The ability of the human immune system to stop infection before it occurs is evolutionarily advantageous on the individual scale, but may negatively impact the population as a whole by enabling viral spread [8].

Viral replication can be broadly classified into six steps illustrated for several common viruses as shown in Fig. 1 [9]. Pathogenesis of a virus includes initial attachment, penetration into the host cell, uncoating, transcription and replication, infection and virion assembly, and release. There are several factors that affect the ability of a virus to both utilize and takeover a host's cellular mechanisms. First, the virus itself must be present in a sufficient load (number of virions), the cells at the infection site need to be permissive, and the human's defense system must be ineffective or absent. Further, viral structure, virulence, replication speed and spread can all affect the course of infection. On the environmental side, temperature, pH, and moisture can affect viral spread. In terms of humans, race, sex, age, and weight of the host have all been shown to play a role in virulence success [10]. Viruses, for all these reasons, present such a risk due to the unpredictability of their behavior in individual hosts (Fig. 2).

Due to the many factors that can affect viral success, there are many options for targeting treatments.

3. Mechanism for nanoparticle delivery of antivirals

In addition to understanding the viral pathogenesis that requires the attention of antivirals to begin with, one must first also understand how most nanoparticle systems actually deliver these drugs. Generally, the nanoparticles are used for targeted drug delivery, as its size and surface properties permit precision; in fact, this is likely the greatest clinical strength of nanoparticles. In order to get to the site of infection, the nanoparticle is inserted into the body intranasally, by mouth, or via I.V. Once it reaches the inflamed or damaged tissue site, the drug can transfer either passively or actively from the extracellular fluid to the intracellular fluid at epithelial junctions. From here, the drug vehicle's targeting depends on surface properties, such as the presence of cell-specific ligands coated on the surface of the nanoparticles. These ligands are often proteins, peptides, antibodies or most commonly, small organic molecules. Once the nanoparticles are received by the targeted cells, channels and other processes permit the appropriate drug through the membrane. This will yield the desired immune response [11].

Organic targeting agents are particularly advantageous due to its chemical stability, low costs and ease of use. On the other hand, the specificity and affinity of these organic materials leave a lot to be desired. Carbohydrates have weak interactions with cell surface receptors but have been proven to be effective in glycotargeting cell-specific lectins. This is supported by using multiple carbohydrates for these interactions to ensure higher efficacy of binding. An example of this is using galactose to bind to asialoglycoprotein receptors [12]. Some alternatives that yield higher affinity without having to use multiple organic agents are biotin (vitamin H) and folic acid (vitamin B9), which are effectively used for binding to streptavidin and endogenous folate receptors. Folic acid-nanoparticle conjugates have merit for cancer treatment [11].

Antibodies are another option as targeting ligands for nanoparticles, and they are mostly monoclonally produced, or taken from mice, rabbits, or humans. These antibodies target extracellular domains (ECDs) and associated proteins, and have proven to be useful ligands for micelles, liposomes, polymers and quantum dots. One drawback from antibody use in ligands is the lack of directionality due to the diversity of functional groups on them. Furthermore, antigen binding, conjugation of antibodies between nanoparticles, and circulation time are all major drawbacks for this type of ligand. However, in efforts to reduce the size of antibodies while keeping the high affinity, fragments have been studied as target-specific ligands. These protein domains are still well expressed, stable and soluble. FN3 (fibronectin III), Z domains and DARPins are all promising in their own rights for their use as ligands on nanoparticles [12].

Peptides are favorable over antibody-based ligands for several reasons, including smaller size, higher specificity, and higher affinity. Some naturally found peptides that have been studied are EGF (epidermal growth factor), cANF, Angiopep-2 and RGD. Peptide-based targeting systems have been successfully conjugated to metallic nanoparticles, micelles, polymers and dendrimers, all of which will be discussed later in this paper. Given all of this, peptides are also limited in vivo, as proteolysis can easily break down these peptides, while observed cytotoxicity and allergic reactions have been observed. Furthermore, peptide-conjugated nanoparticles lack oral bioavailability, and are more costly than the other types of ligands [12]. Overall, all these different types of ligands are used to target and bind to specific cells while yielding their own specific advantages and disadvantages.

4. Issues with current antivirals

As is clear with the present state of HIV, the life of those with chronic viral infections has been greatly improved. However, with the onslaught of new strains of the flu each year and the emergence of new viruses around the globe, challenges are being presented to current antiviral therapies at a magnitude previously unseen. One of the major challenges associated with antiviral drugs is bioavailability, affected by a drug's

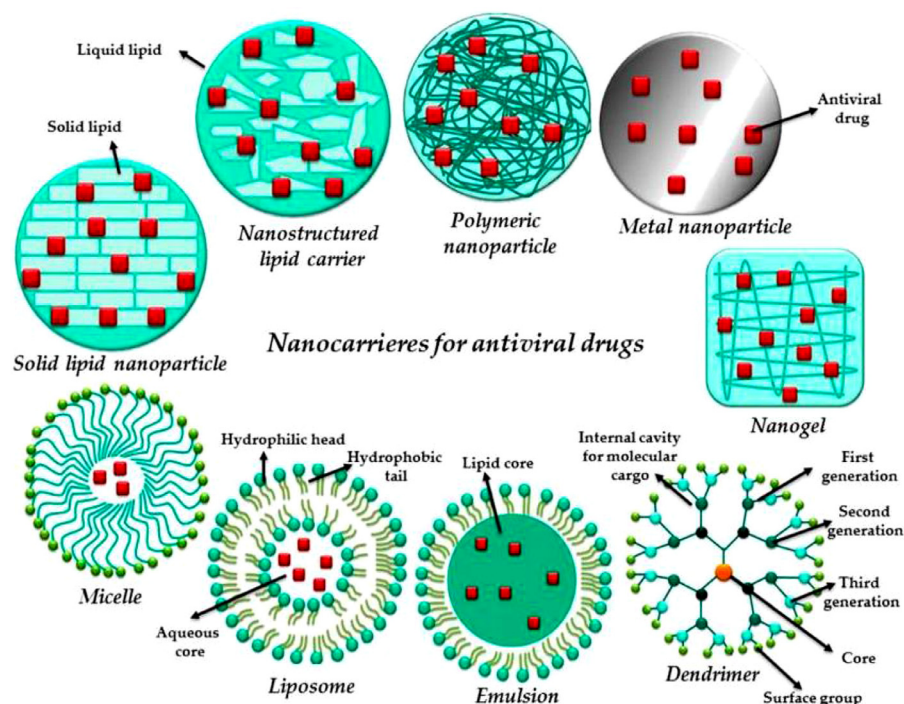


Fig. 2. Structures of a selection of relevant nanoparticulate carriers for targeted antiviral drug delivery [3].

ability to be absorbed by the gastrointestinal tract. In the antiviral acyclovir, some patients presented absorption rates as low as only 15% of the administered drug [13]. The bioavailability is affected by solubility and permeability. Consequences associated with low bioavailability are a higher required dose, which may lead to toxic effects. The delivery method of the drug is typically oral, but researchers have explored topical and intravenous methods to increase bioavailability. These routes present their own dangers. Not only is delivery method important, but many viruses reside in hard to access reservoirs such as the lymphatic system or synovial fluid, both of which current antivirals cannot reach.

In the case the drug is permeable and able to reach the virus, many common carriers are not selective enough to guarantee a targeted release of the drug. This can lead to prolonged drug exposure which presents more risk of developing drug tolerance or resistance, particularly in severely immunocompromised patients. In addition to low bioavailability, the half-life of many antivirals is short. If the half life is short, the frequency of administration may need to be increased. Studies have shown that frequently administered drugs lead to patient non-compliance and excessive cost [13]. More risks for the patient include negative interactions with prescription drugs. As efficacy of current drugs has remained problematic and the understanding of viral mechanisms has increased, the scientific community has looked to nanotechnology as a potential solution.

5. Nanotechnology

Almost any particulate carrier which is currently used as a vehicle for antiviral drug therapy can be nano-scaled. The smaller sizes of these same carriers address many of the aforementioned problems. A list of the advantages of using nanotechnology to nanoscale antiviral drug delivery carriers is shown in the table below.

Table 1.

The positive outcomes from a public health perspective are obvious, but the financial gains provide all the more reason nanotechnology should be advanced in the drug delivery field. In 2007, the nano-based drug delivery was worth 3.4 billion USD [13]. In an October 2020 report from iHealthCareAnalyst, inc., it was predicted that by 2027, the global

Table 1

A summary of the advantages of using nanotechnology to solve common issues with drug delivery.

Nanoscale Drug Delivery Advantages	
Improved bioavailability	Decreased drug resistance
Controlled Release	Overcome cell barriers
Protection of drug	Site-specific targeting

market would soar to a value of 152 billion USD [14]. Major biotechnology companies have opened the door to a vast field of research and applications regarding nanotechnology.

5.1. Carbon based polymers

Carbon-based nanomaterials including graphene, carbon dots (C-dots) and fullerenes have all proven to be potentially helpful materials for treating patients via antiviral delivery. This is due to their characteristically low cytotoxicity, as well as the ease at which researchers can alter the properties, which can specify the function of the nanoparticle itself. For example, graphene has proven to be effective in direct interaction with viruses. Carbon dots (on the scale of 10 nm) can be used for a range of varying viral responses, while fullerene has demonstrated inhibitory effects on viral activity. Ultimately, each of these carbon materials have different applications for nanoscale antiviral treatment (Fig. 3) [15].

5.1.1. Graphene oxide

Graphene-based nanomaterials, especially graphene oxide, have been used in treating bacterial activity. Graphene oxide (GO) and reduced graphene oxide (rGO) damage the membranes of non-local bacteria, while *E. coli* tends to be wrapped and destroyed by the material. In terms of its application for antiviral activity, experiments were run using RNA and DNA to treat the porcine epidemic diarrhoea virus, or PEDV. Graphene oxide's sharp edges nullifies the virus prior to its interaction with cells. In addition to the sharp edges that permit penetration, the negative charge of GOs allows electrostatic interaction with

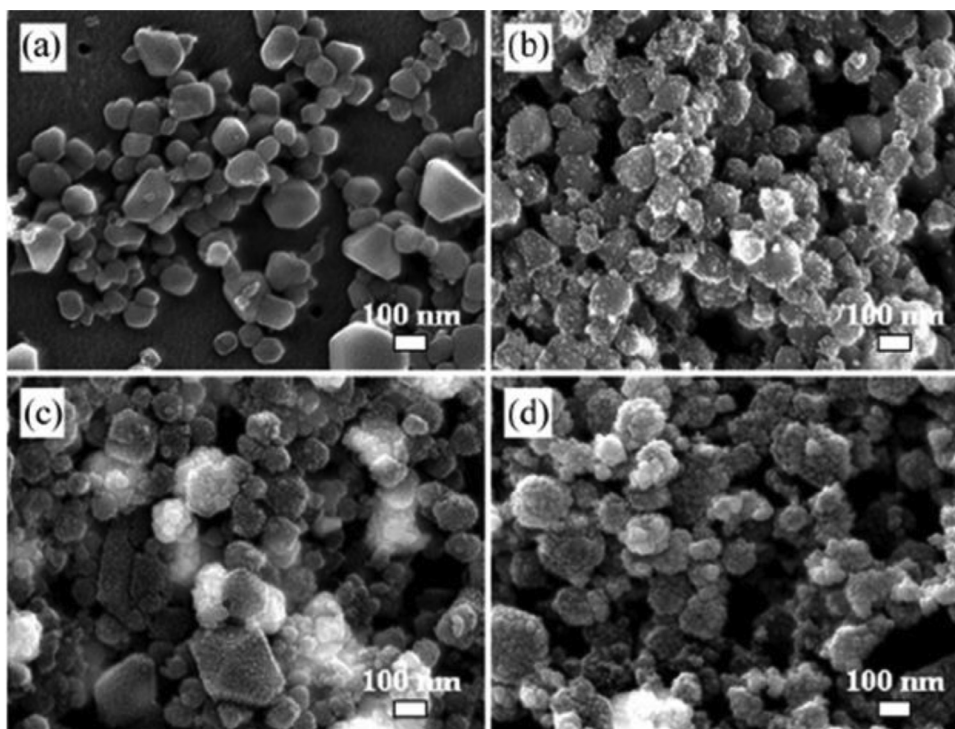


Fig. 3. SEM image of carbon-60 based nanocrystals formed using: (a) precipitation with gold coating, at (b) room temperature, (c) 40°C and (d) 80°C [2].

viruses which increases binding, permitting more effective antiviral activity. Additionally, photocatalysis can be performed by graphene oxide, which directly causes photodegradation of viruses. This enhances the degradation caused by the sharp edges.

Graphene oxide nanoparticle systems that are enhanced by silver also show increased degradation of viruses. This is because the silver (Ag) increases binding to the glycoproteins on the membrane of the viruses, which is a preventative measure before the viruses invade cells. This has shown effectiveness in other coronavirus variations including the feline coronavirus and infectious bursal disease virus. Other ways that graphene oxide-based materials have proven to be effective as antiviral treatments is by mimicking the cell surface as platforms for antiviral drugs, and by using the search and destroy strategy. Graphene oxide-based material bound by heparan sulphate and other sulfonated groups have shown the capability to mimic the surface of cells that share their chemical properties. The effectiveness of this method is dependent on a number of factors including the number of layers, surface wrinkling, geometric topology, and size, which all are directly correlated with the binding affinity with the targeted viruses. Once the virus is bound to the material, magnetic nanoparticles can be deployed to inactivate the virus by emitting infrared radiation. This method has shown some promise to treat respiratory syncytial viruses (RSV). An alternative treatment is to use these materials as a 2D platform where drugs can be loaded onto. For example, hypericin (HY) can be attached to graphene oxide materials to treat hepatitis B through physisorption and other hydrophobic interactions. This method is advantageous compared to other treatments, as the cytotoxicity is remarkably reduced [15].

5.1.2. Carbon dots

Carbon dots are another carbon-based material, more recently discovered as an option for nano-sized antiviral delivery. Also known as C-dots, these nanomaterials consist of the following types: amorphous carbon nanoparticles, partially graphitized core-shell carbon nanoparticles, amorphous fluorescent polymeric nanoparticles and graphene quantum dots (GQDs). Each of these materials have potential in treatments for viral infections due to their surface-based functional groups. C-dots made from boronic acid have shown promise in treating *Herpes*

simplex virus type 1 (HSV-1). This same study also confirmed low cytotoxicity associated with C-dots, as well as its preventative properties against virus-cell interactions. Alternatively, C-dots enhanced by anhydrous citric acid, and only around 3 nm in diameter, have shown to be effective in treating HIV-1. This is mainly due to the hydroxyl and carboxyl surface groups as well as the boronic acid which work together to inhibit hydrogen bonding between the viruses and the cells [15].

5.1.3. Fullerenes

Fullerenes, which are the earliest discovered carbon-based nanostructures, have been researched as potential antiviral treatments ever since its discovery in the mid-1980s. One application that is commonly associated with this specific material is antiviral treatment against HIV. This is generally accomplished by blocking encoded enzymes through inhibiting active sites of the HIV protease. Fullerenes are a particularly good fit for this application, and diamido diacid diphenyl fulleroid is one synthesized material used for this exact purpose. Generally, fullerenes also exhibit low cytotoxicity. The main disadvantage associated with fullerenes is their low solubility. This is compounded by the difficulty of using surface modifications in synthesis to make them more soluble. To increase solubility, they can be enhanced in combination with highly soluble materials like alkali metal salts. However, this complicates the synthesis process further in both time and resources. Fullerenes are capable of generating singlet oxygen particles, which have been shown to cause photodynamic inactivation of some viruses. Carbon-60 based materials are particularly effective as photosensitizers. Since this can potentially increase cytotoxicity, the decreased solubility observed in fullerenes and associated materials is actually an advantage, as this allows easier removal from the body. Overall, fullerenes show promise in treating several diseases, including hepatitis C virus (HCV), respiratory syncytial virus (RSV), H1N1, herpes simplex virus, human cytomegalovirus, Zika, and Dengue viruses [15].

5.2. Cyclodextrin-Based delivery systems

Because of its ability to deliver drugs with an associated spread-rate to a specified site of the body, cyclodextrin-based delivery systems offer

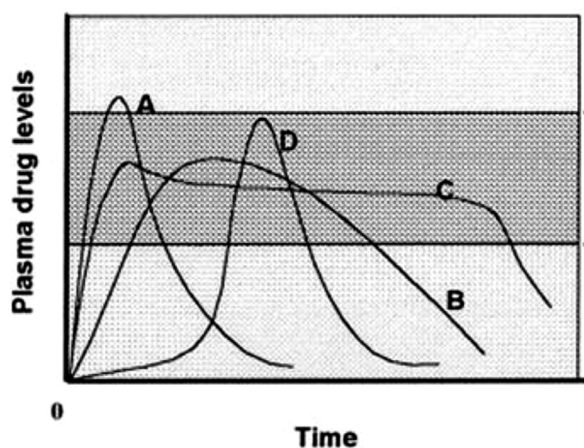


Fig. 4. Plasma drug levels observed in the body over time for different release patterns including: (A) Immediate release, (B) Prolonged release, (C) Modified release, and (D) Delayed release [16].

themselves as a very promising vessel for antiviral drug therapy. One specific characteristic of cyclodextrins (CDs) is that they can form hydrophobic inclusion complexes in solution and in solid state. As a result, delivery systems made of this specific biomaterial can have its physical properties easily altered. The standard form of cyclodextrins, β -CD, contain a total of 21 hydroxyl groups including seven primary and fourteen secondary hydroxyls. These hydroxyl groups lend themselves to be the starting point for the addition of functional groups that will give the modified material varying chemical properties. Because of its flexible physical and chemical properties, cyclodextrin-based delivery systems are a promising means of antiviral drug delivery [16].

With the use of CDs, there are several types of release patterns associated with different goals of the drug delivery including immediate, prolonged, modified, and delayed release. Immediate release cyclodextrins are especially useful for the injection of drugs in emergency scenarios, as it provides an increased dissolution rate for drugs that are not very water-soluble. Some modified cyclodextrins used for this are HP- β -CD, DM- β -CD, SB- β -CDs and branched β -CDs. While immediate release cyclodextrins are generally associated with drugs with low water solubility, prolonged release is used for water-soluble, high dose drugs that need to be released into the body over a certain amount of time. Generally, this type of delivery is advantageous in that it can reduce the frequency of administering doses to patients, as the release of a larger single dose can be spread over a larger amount of time. Furthermore, the specific types of cyclodextrins that are associated with prolonged release are ethylated and acylated β -CDs (Fig. 4) [16].

Modified release mechanisms, which generally consist of a combination of different cyclodextrins, is generally associated with the encapsulation of drugs that need to be released into the body constantly over a period of time. Furthermore, modified release is used for drugs that have poor oral bioavailability as well as decreased solubility due to the formation of crystals. However, using cyclodextrins in combination with HCO-60 actively prevents this characteristic crystal growth, while the addition of hydroxypropyl cellulose (HPC) allows the dissolution of the drug to reach a relatively steady rate within the body. For drugs that need to be released in a specific part of the body, like the intestines (enteric preparation generally used), delayed or time-controlled release can be used to target a part of the body by calculating the time it takes for the drug to travel there and be metabolized [16].

Two other types of drug release patterns that can be observed through a combination of other methods include pH-dependent release and site-specific release. pH-dependent release used for drug efficacy is dependent on the acidity or basicity of the drug itself and the environment the drug is being released into. Site-specific release on the other

hand, is generally associated with delayed release into the colon or the brain, where pH dependency and time factors must also be considered. Overall, cyclodextrin based delivery systems offer a flexibility of drug release that is overwhelmingly relevant to antiviral therapy in the body [16].

5.3. Micelles

Micelles are another promising method of antiviral delivery as a vehicle for drugs that require prolonged blood circulation time, cellular selectivity, and controlled release delivery. The micelle structure generally contains a core hydrophobic block copolymer, and a corona shell that is the hydrophilic component of the same copolymer. One application for micelles is for the delivery of acyclovir (ACV), a drug commonly used to treat herpes, the varicella zoster virus and the Epstein-Barr virus [17].

Previously, hydrophilic polymers and other drug carriers had been used to encapsulate the acyclovir as a means of solving the drug's low solubility and bioavailability. However, these methods are costly and difficult to produce in a timely manner. Alternatively, in one study conducted by Sawdon et al., polycaprolactone (PCL) was used as a means for acyclovir drug delivery. To understand the structure of the final product of this antiviral delivery material, it is important to first discuss the structure of the original polycaprolactone. PCL's chemical structure is linear, resorbable and aliphatic, while its physical structure is semi-crystalline. Furthermore, PCL is biodegradable, and generally biocompatible, making it a very convenient vessel for drug delivery [17].

Generally, PCL is enhanced using alcohol as an initiator, but acyclovir actually acts as a replacement in this case, implementing itself into the structure of the polymer itself. This is because in the reaction between PCL and acyclovir, ACV can act as a ring-opener to polymerize ϵ -caprolactone (ϵ -CL) which forms the resultant ACV-polycaprolactone (ACV-PCL). In this case the ACV replaces alcohol, as well as methoxy-poly(ethylene oxide) and starch (which act as macroinitiators), as the initiator for the chemical reaction. With the simplicity of the production, this approach is cheaper and simpler than the previously used encapsulation methods for acyclovir.

To enhance the physical properties of this vessel, methoxy-poly(ethylene glycol) (mMPEG) or chitosan is grafted onto the ACV-PCL to form a block copolymer. While the mMPEG polymer is biocompatible, hydrophilic, inexpensive, and non-toxic, the chitosan polysaccharide (derived from chitin) is naturally occurring, biocompatible, and biodegradable. With the diverse properties offered by the MPEG and chitosan respectively, the polymers generally assemble aqueously, and the final product is an effective nanocarrier. Within the study being discussed, both ACP-PCL-mMPEG and ACV-PCL-chitosan micelles were synthesized and studied. It is noteworthy to emphasize that the ACV polymerization method being discussed was advantageous by eliminating numerous drug loading steps, increasing the carrying capacity of the vessel, and by decreasing cost significantly. Both variations were non-toxic to the colorectal cells that the ACV was being used on, and the synthesis formed singular carriers that were roughly 200 nm or less. Overall, despite being less expensive and less time consuming, the use of micelles for acyclovir delivery is a viable option [17].

5.4. Exosomes

Exosomes are another potential vehicle for antiviral drug delivery, derived from vesicles secreted by cells in the human body. Through observation, it has been noted that during viral infections of the body, namely from the influenza virus, these vesicles alter their makeup to express antiviral proteins. The response of the body to these exosomes ranges from promoting inflammation of the pulmonary system, to actively inhibiting viruses from binding and intruding pulmonary cells [18]. Due to these innate responses to viruses, exosomes are another promising nanoscaled candidate for antiviral treatments.

Exosomes are yielded through endocytic pathways and are generally found to be between 30 and 100 nm in diameter [19]. In normal circumstances where the body is not virally infected, exosomes act as a carrier between cells, and are released regularly for this purpose. They are known to be vehicles for transporting proteins, lipids and RNAs between cells, and can be found in most types of bodily fluids. However, in addition to the proteins from the cell they originated from, and the biological cargo in which they are carrying, exosomes are also rich in other proteins. These include tetraspanins (such as CD9, CD63, and CD81), heat shock proteins and Rab proteins [18].

In terms of their response to viral infections of the body, exosomes have shown differing responses. For example, if it is produced by an infected cell such as one with the immunodeficiency or hepatitis virus, exosomes could actually foment the infection process. This is an undesirable scenario that is obviously preferred to be avoided. Alternatively, and more favorably, exosomes can express interferon-induced (IFN) antiviral proteins which have been shown to disrupt viral replication and reinforce the defenses of yet-to-be infected cells. One example of an effective interferon for viral defense is Type I IFN, which, if spread to other cells, promotes resistance to the Hepatitis B and Dengue Viruses. Furthermore, exosomes can bind to epithelial cells, also inhibiting the viral invasion of influenza [18]. Ultimately, exosomes exhibit many promising traits that, given alterations, could be a very strong candidate for antiviral drug delivery in the body.

Although all of these applications certainly show promise, it is important to note that most of what is known about exosome antiviral response is from *in vitro* studies. In other words, further inquiry into *in vivo* studies would be required to confirm exosome effectiveness in human bodies. To accomplish this, Bedford et al. conducted research on mice, and concluded the following from the study: exosome protein composition evolved during viral infection; exosomes from infected mice intranasally inserted into healthy mice evoked pulmonary inflammation; exosomes containing antigens for the virus served as a source for other infected areas; and some exosomes attached themselves to healthy cells to block viral infection. The evocation of pulmonary inflammation in healthy mice was particularly intriguing, especially when considering the study controlled this phenomenon by inserting exosomes from other mice injected with inflammatory adjuvants [18]. Given the widespread utility of exosomes in mice infected with influenza, they are certainly a promising candidate for fighting influenza in humans, which is still a cause of death for countless people around the world.

5.5. Lipid polymer

Lipid-polymer based delivery systems are a particularly promising vehicle for messenger RNA (mRNA) therapeutics, such as vaccines, cancer treatment, protein replacement therapy and genome editing. Because mRNA is unstable and lacks reliable translatability, this type of antiviral treatment is reliant on properties derived from lipid-based carriers commonly known as lipid nanoparticles (LNPs) or lipid-like nanoparticles (LLNs). Many LLNs used for antiviral delivery are derived from N1,N3,N5-tris(2-aminoethyl) benzene-1,3,5 tricarboxamides (TT), including the most commonly used TT3 LLN, which is used for mRNA delivery. One study looked into the use of different PLGAs (PLGA4-7) as additions to the TT3-LPNs being used for antiviral mRNA delivery [20].

The results showed that each of these PLGA enhanced LPNs showed significant improvements to the existing mRNA delivery systems of TT3-LLNs. Because of the introduction of hydrophobic polymers, the transfection efficiency was drastically enhanced compared to the existing treatments. These PLGAs contained molecular weights between 24,000 and 38,000 g/mol with viscosities between 0.32 and 0.44 dL/g. Of the PLGAs used, PLGA4 was the most notable, with better mRNA delivery efficiency compared to PLGA5, PLGA6 and PLGA7. Specifically, improvements were observed in the zeta potential, encapsulation efficiency, and delivery efficiency for prolonged time points. These traits favor PLGA4

enhanced LPNs that would be used for sustained release of mRNA treatments in these specific nano-vessels (Fig. 5).

Based on the promising results from these experiments, further research into the use of lipid-polymer enhanced nanomaterials is certainly inevitable [20].

5.6. Liposomes

Another subset of lipid-based nanoparticles are liposomes. Liposomes are small, spherical phospholipid bilayers that enclose an aqueous core. On average, liposomes are somewhere in a size range of 15–1000 nm. The aqueous core entraps the drug to be delivered until its release, triggered either by passive or active targeting. The primary distribution of the drug bearing liposome into the tissue is passive. However, active targeting becomes the predominant mode of recognition as the liposome approaches and comes within a Van Der Waals radius of the target cell. Attaching site specific ligands or amino acids fragments, such as antibodies, proteins or other appropriate fragments to the liposomes surface achieves active targeting. One reason for the relevance of liposomes is as a potential mechanism for improved antiviral delivery. Because of the structure of their bilayer, liposomes can transport large drug loads of either hydrophobic or hydrophilic nature. The liquid layers of the liposome behave as protection for the drug from gastrointestinal degradation and other metabolic processes. Being protected increases its efficacy and bioavailability, two major concerns with current antiviral delivery methods [21].

Preparation techniques common for producing liposomes include both passive and active loading techniques, supercritical fluid, dual asymmetric centrifugation, membrane contactor technology, crossflow filtration, freeze-drying, detergent removal, solvent dispersion, and mechanical dispersion with sonication. Transmogrification of the lipid bilayer composition can create other desirable properties such as a prolonged half-life, resulting in a “stealth liposome,” and delivery of its contents to the cytosol through way of the endosomal or lysosomal pathways. A final alteration to improve the liposomes is the addition of a surface coating of a hydrophilic carbohydrate or polymer (lipid derivative of PEG) [21].

Further applications of liposomes are based on their classification as either cationic or pH sensitive. Both properties can facilitate DNA encapsulation, form a stable complex, and deliver it to target cells. The inspiration and logic for the design of pH-sensitive liposomes originates from viral fusion with the endosomal membrane, therefore delivering foreign genetic material to the cytosol before it reaches the lysosomes [21].

Despite their ability to carry such a vast range of cargo, be targeted for site specific delivery, and protect sensitive drugs from metabolic processes enhancing bioavailability, there are some drawbacks to liposomal delivery methods. One major disadvantage is the liposomes' rapid clearance from the blood because of the adsorption of plasma proteins in their sterically stabilized, second generation form. Besides this, there are some physical instability related issues in which leakage or fusion may affect drug storage or administration to the liposome [21].

5.6.1. Solid lipid nanoparticles

A system similar to the liposome, but differing in its aggregation status of lipids, are solid lipid nanoparticles (SLN). These colloidal systems comprise a solid lipid matrix ranging across an even broader size spectrum of 10–1000 nm. Some solid lipids that make up the matrices include but are not limited to, triglycerides, partial glycerides, steroids, fatty acids, and waxes. SLN's can be functionalized and are therefore capable of targeted drug delivery. Else, SLN's can achieve a controlled drug release profile, and have an increased load capacity and stability as compared to liposomes. Preparation occurs in a variety of manners such as high-pressure homogenization, solvent emulsification/evaporation, emulsification–diffusion, fluid extraction of emulsions, ultra-sonication,

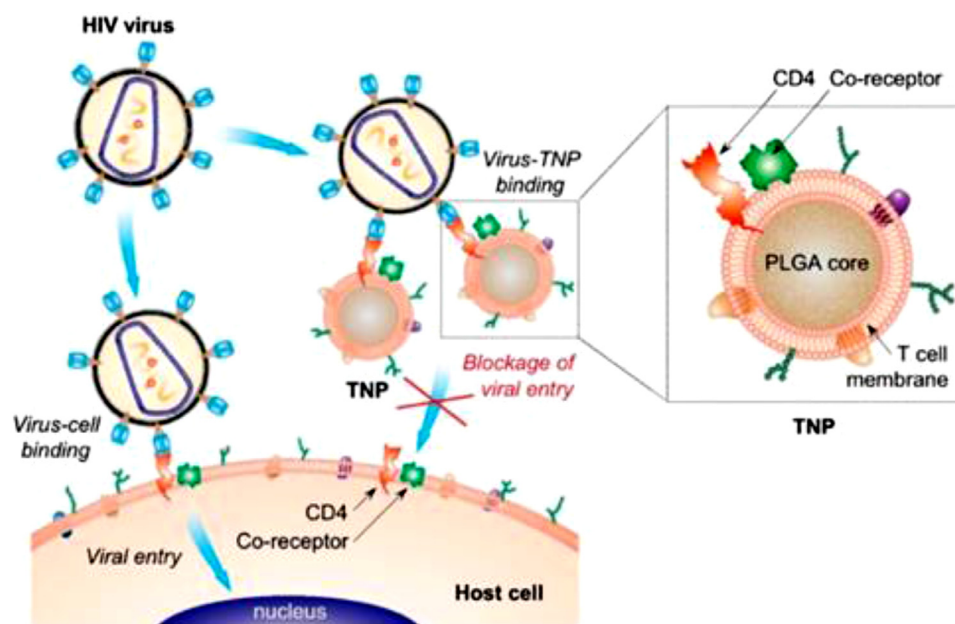


Fig. 5. Use of a T cell membrane modified nanoparticle containing a PLGA core to deplete viral infection [2].

supercritical assisted injection in a liquid antisolvent, and spray-drying [22].

At present, SLN's are used as the delivery mode of the FDA approved antiretroviral drugs for treatment of HIV/AIDS like ritonavir, maraviroc, darunavir, efavirenz, zidovudine, and lopinavir. Studies of these drugs when using SLN's as the delivery method have shown improvements in the following characteristics: permeability, bioavailability, retardation of P-gp efflux, cytochrome P450 metabolism, increased lymphatic system uptake, prolonged release, and better distribution throughout the body's tissues [23]. One more critical trait to their use and applicability on a mass scale, is that SLN's have been proven to be industrially scalable [24]. There is a second generation of SLN's called nanostructured lipid carriers, which use liquid lipids instead of solid to form their matrices. They are capable of surface modification for target specificity and are even preferred over SLN's for their better loading capacity, stability and controlled release patterns [1].

5.7. Polypeptides

Polypeptides are another auspicious nanoparticle that can be used to produce an immune response in individuals infected with a virus. In particular, elastin-like polypeptides, or ELPs, have shown promise in this regard. This is attributed to their lower critical solution temperature phase transition behavior (LCST), which grants the substance solubility below a specific temperature, known as its cloud point (T_c). Above this temperature, however, ELPs form micron scale coacervates that can be used for viral treatment. These phase changes are easily reversible over small-time frames [25].

Elastin-like polypeptides are synthetically produced with repeating lines of genes, often made through a process known as concatemerization, which permits the desirable genes containing cohesive ends to ligate to one another. The major drawback from this method, however, is that it makes the total molecular weight imprecise. This in turn, may impact the utility of the nanocarrier. That is why many ELP gene sequences yield polymers of less than 30 pentapeptides and are often seen in combination with other materials. In these chains of elastin-like polypeptides, repeating links of valyl prolyl glycyl valyl glycine (VPGVG) are generally observed [26].

Furthermore, ELPs can be genetically encoded to produce sundry biochemical structures of these homogenous monodisperse polypeptides, which in turn permits ELPs the potential for numerous antiviral appli-

cations. The size of these elastin-like polypeptides ranges greatly, as they can be nano, micro, and macro-scaled carriers for drugs. In addition to the range of sizes, ELPs can be used as depot carriers for peptide or protein-based drugs, and can be adjusted for different release patterns, including disease targeting [26]. Because of the versatility and novelty of ELPs, increased research and use of it should certainly be expected in the coming years.

However, despite this versatility, it is important to note that ELPs and their applications have hardly come close to realizing their full potential in the field of molecular biology. For one, ELPs are a promising tool for potentially adding substances into biopolymers, such as unnatural amino acids. Moreover, supplemental research is required to fully realize the limits of ELP gene synthesis and expression, as well as its potential contributions towards cloning, translation and post-translational modifications. ELPs have additionally been observed to be useful components to other antiviral nanostructures such as vesicles, nanofibers, dendrimers, and nanoworms. Further analysis of the morphology of ELPs would benefit all of these vehicles, and ELP applications. By better understanding the molecular arrangement, further research could fine-tune them, and potentially increase their efficacy. Lastly, polypeptides that exhibit alternative properties such as upper critical solution temperature phase transition behavior (UCST) require further inquiry to fully evaluate and understand their prospective utility [26]. Overall, between the current knowledge regarding ELPs, and its predicted potential novel applications, polypeptides are certainly an intriguing branch of nanomaterials.

5.8. Dendrimers

Dendrimers serve as another promising option for antiviral drug delivery as well as gene therapy, and as a vessel of transportation into and throughout the body. Dendrimers are highly branched polymers that consist of a central moiety, repetitive monomer sequences known as dendrons, and surface groups on the outermost parts of the polymer. Given the branch formation of dendrimers, the structural formation is relatively spherical. Thus, the size is generally considered in terms of its diameter, which is scaled in nanometers. Two examples of dendrimers are the G4 and G5 polyamidoamines (PAMAM) which have diameters of 4 and 5 nm respectively. Generally, most dendrimers have diameters ranging from 2 nm to 10 nm and are monodisperse in terms of their molecular structure. The surface groups allow for additional functional

groups to be added, altering the carrier's chemical composition. Since the central moiety is hydrophobic and charged, they have relatively high water solubility and attract hydrophobic drugs more readily. In other words, with control over the composition of the innermost hydrophobic core's structure, it is possible to alter absorption and distribution rates of the hydrophobic drugs [27].

Some existing antiviral applications for dendrimer systems include treatments for the influenza virus, human immunodeficiency virus, and respiratory syncytial virus. Dendrimer treatment effectiveness for these antiviral applications is a result of the diverse functional groups that are found on the surface which can block viruses from entering the cells. Despite the highly effective nature of dendrimer treatment in early stages of viral infection (specifically during the phase of infection where the virus adsorbs to the surface of the cell), effectiveness drops dramatically once the viruses enter the cell [27].

One study regarding dendrimer applications for medicine specifically focused on carbosilane dendrimers and their potential viability for treating tumors and viruses, in addition to being used for gene therapy and drug delivery. Dendrimers can have their properties determined by several different factors, specifically generation numbers (which determine molecular weight and molecular size), and the structure of the dendrimer's core and outer branches, which can be charged anionically or cationically to create artificial water solubility for the drug. These charged outer branches allow other charged groups to electrostatically connect to the existing dendrimer. This is actually a phenomenon that is observed between positively charged carbosilane dendrimers and negatively charged nucleic acids, which form dendriplexes. The structure is advantageous as it protects unwanted degradation of the nucleic acid contents, which in turn increases the quantity that reaches targeted cells. Thus, this method of antiviral delivery is particularly applicable for potential research into HIV treatment and other RNA-based viruses like SARS-CoV-2 [27].

As well as being a potential option for treating HIV, dendrimer-based antiviral treatment has potential for treating MERS-CoV, also known as the Middle East respiratory syndrome. This is relevant because of similarities that can be drawn between MERS-CoV and SARS-CoV (COVID-19). Both illnesses are of the respiratory system, originated in wild animals, and can be easily transferred between humans. Instead of originating in Wuhan, the Middle East respiratory system originated in the Arabian Peninsula. In one study, 16 dendrimers were used in conjunction with an antiviral treatment for MERS-CoV and were tested by mixing the product with the virus itself. There was a substantial decrease in viral activity, specifically in the variations of G(1.5)-16COONa and G(5)-128SA which yielded a 40% decrease in viral plaque formation. Ultimately, dendrimer-based antiviral treatment is of particular relevance, with its potential connection to the ongoing global pandemic [28].

5.9. Nanoemulsions

Nanoemulsions are thermodynamically stable systems existing in a single phase that consist of oil, water, surfactants and co-surfactants. Nanoemulsions, depending on the size of encapsulated drug particles, mechanical energy, composition and relative amount of the surfactants, can be between 20 and 500 nm in size. They can be classified in one of three categories. The first is oil in water (O/W), in which oil droplets, composing 5–20% of the system, are dispersed in continuous aqueous phase. Second, water in oil (W/O), an emulsion where water droplets are dispersed in continuous oil phase. The third, bi-continuous nanoemulsions where microdomains of oil and water are inter-dispersed within the system. As aforementioned, the systems also contain surfactant molecules. These surfactants have two parts: a hydrophilic head and a hydrophobic tail. Surfactants are classified based on the polar groups present in their head and lead to three further classifications of nanoemulsions. These are, neutral O/W nanoemulsions, cationic O/W nanoemulsions, and anionic O/W nanoemulsions. Sometimes the addition of a second co-surfactant can help to facilitate the stabilization process. Nanoemul-

sions are typically prepared in one of five ways, low-energy emulsification, phase inversion temperature, ultra-sonication, high pressure homogenization, or microfluidization. The oil components are frequently soyabean, castor, and peanut [29].

Nanoemulsions have shown to hold certain advantages over conventional emulsions that include but are not limited to: increased aqueous solubility, loading capacity, residence time in GIT, lymphatic uptake, and enhanced absorption and bioavailability. The oil composition of nanoemulsions enables them to be absorbed in the gastrointestinal tract, therefore increasing bioavailability of protein based drugs loaded inside of them [29]. Drug solubility, rate of absorption, and targeted drug delivery are common matters of concern in antivirals. Nanoemulsions can solve these in one step because of their extremely small particle size. Due to their size, and ability to solubilize both hydrophilic and lipophilic drugs, dissolution is improved and therefore solubility of both hydrophilic and lipophilic drugs. Their size enables controlled optimization of dosing, decreasing drug toxicity. Small size also allows for effortless penetration of the epithelial layer, which improves absorption rate. This overcomes the primary issue with topical antiviral delivery. Nanoemulsions with a positive charge were determined to penetrate the epithelial layer better than those with a negative charge because of their utilization of skin's negative charge to penetrate [1]. Studies involving the drug Manyarara found that using a nevirapine nanoemulsion the drug efflux was far lower; the drug had a better release profile and permeability than the drug in its pure state [30].

5.9.1. Self-nanoemulsifying drug delivery systems

A class of nanoemulsions called self-nanoemulsifying (SNEEDS) are lipid-based monotropic systems formed spontaneously by the emulsification of oil with water through the help of surfactant or solvent and the application of gentle stirring. These are used to solubilize hydrophobic drugs in the oil phase. Like their nonspontaneous cousins, these systems are also thermostable and nanosized. They enable further improvement in the penetrative capabilities and bioavailability of the system [1]. Antiviral drugs such as Capryol 90, Lauroglycol 90, and Capmul MCM all use these systems. When Nevirapine (an HIV antiviral) was produced as SNEEDS, the study found that it released 98.9% in the aqueous portion of the GIT as opposed to only 14.74% in a drug solution, a stark improvement in released dosage [31].

5.10. Nanogels

A nanogel is a hydrogel on the nanoscale that can be used for retroviral drug delivery. Hydrogel's three-dimensional cross-linked polymer network has unique properties, enabling them to swell and be composed of up to 95% water (at which point they are considered superabsorbent) without ever dissolving into an aqueous medium. It can be made of natural, synthetic or a combination of both polymers. The properties exhibited by a nanogel combine the behavior of the solids and fluids and depend on the contributions of each portion. The liquid portion's presence keeps the nanogel from becoming a compacted insoluble mass, while the solid portion prevents the liquid from free flow. Chemically cross-linked polymers can be prepared through heterogeneous polymerization reactions in the presence of either bifunctional or multifunctional cross-linkers. This includes the living radical polymerization techniques which allows for formulation of NG's with different composition, dimensions, and architectures, including core-shell and hollow nanogel particles. Incorporating functional initiators and macroinitiators further allows functionalities in the interior or on the surface of nanogels. The size, charge, porosity, amphiphilicity, softness, and degradability can be further fine-tuned by varying the nanogel's composition [32].

Nanogels, because of their composition, exhibit several properties of value in antiviral delivery. These include high encapsulation efficiency and protection of active agents from degradation. Due to their hydrophilic nature, they are highly biocompatible and can incorporate a plethora of cargo drugs. Unlike many other delivery nanosystems, they

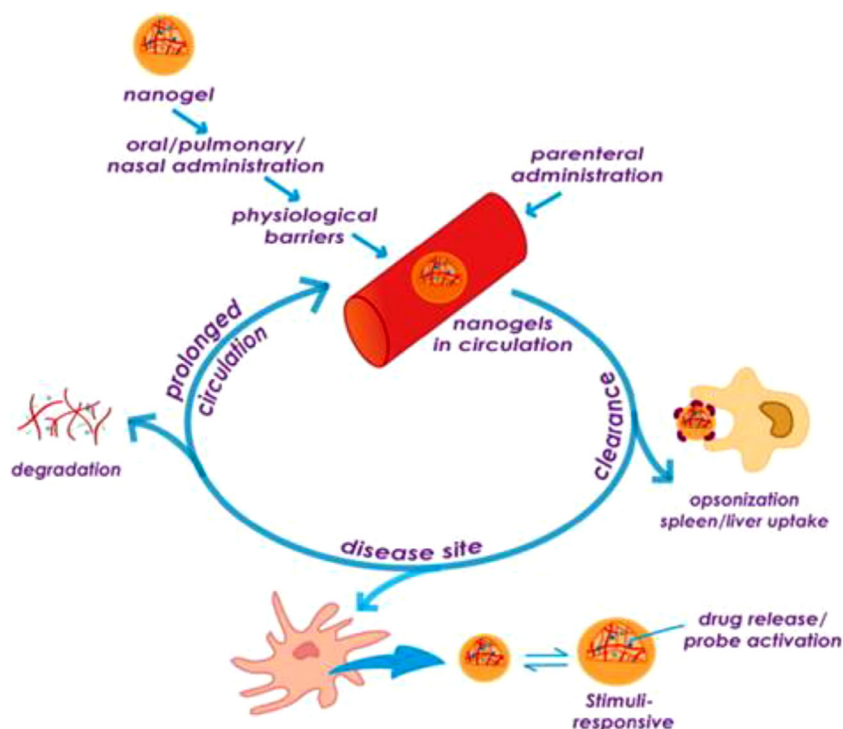


Fig. 6. Depiction of nanogel advantages including multiple administration modes, stimuli-responsive release, and prolonged circulation due to protection from degradation [32].

are highly stable and also multifunctional, meaning they can be used for both diagnosis and treatment of viral infection. This trait is seen in few other types of delivery systems. Nanogels can also be specifically targeted, either actively in conjunction with a target ligand, or passively [32].

Nanogels are also stimuli responsive. Internal or external stimuli such as pH, temperature, magnetic field, enzyme concentration and redox environments among others govern their behavior. The stimulus will cause a conformational or structural change in the NG, which can manifest in the form of swelling or deswelling of the nanogel network, leading to responses like release of the entrapped antiviral. This makes it an ideal candidate for an antiviral, as viruses have been shown to create environments in which the pH is unnaturally low. Thus, a pH sensitive nanogel could be targeted to a viral reservoir and release of its cargo mediated by the low pH induced by viral presence. In one study, thermo-precipitation synthesized thermo-responsive PVCL NGs in aqueous phase through free radical polymerization. The nanogel showed an antiviral effect of PVCL804 NG against the HIV-1 infection by quantification of luciferase activity, as administered vaginally (Fig. 6) [33].

Moreover, addition of a PEG coating on the surface of the nanogel makes it more hydrophilic and gives the gels a stealth property. This shields any charge that the core of the gel may carry due to its cargo and decreases the probability of interactions with any serum proteins it may encounter. Some issues in need of addressing before widespread application of nanogels for antiviral systems are the controllability of stimuli-responsive release rate, degradation kinetics (biocompatibility), and stability [1].

5.11. Nanocrystals

Because roughly 40% of new drugs are poorly soluble in water, a major focus in drug delivery research is to find biomaterials that will permit appropriate dissolution of the drug with solid efficacy. While immediate-release applications of cyclodextrin-based delivery systems appear to be a promising vehicle for this purpose, nanocrystals have recently been discovered as an equally applicable solution. Nanocrystals

were invented in the late 1990s and are generally measured to be between 100 and 1000 nm. These nanocrystals, unlike the other drug-carriers mentioned throughout this paper, are not considered carriers at all: they only consist of the pure drug being administered and very small amounts of surface-active agents to stabilize the structure. After processing these crystals, the nanocrystals can easily be physically altered in the form of existing drug-delivery forms such as tablets [34].

In order to create nanocrystals via precipitation, there are several factors that need to be considered that directly influence the properties of the final product: stirring rate, ratio of antisolvent to solvent, drug content and temperature. As stirring rate increases, the particle size decreases, creating a homogenous tablet. The antisolvent-to-solvent ratio determines the saturation of the drug within the nanocrystal, with a larger ratio creating a more concentrated resultant. In addition to this ratio, the quantity and properties of the drug that is being worked with will determine the viscosity and homogeneity of the material. Temperature during the production of nanocrystals will impact the size of the crystals as well, with a lower setting temperature creating smaller individual particles in the aforementioned range of 100–1000 nm [34].

Alternatively, nanocrystals can also be produced through pearl milling techniques, where properties are defined by the drug amount, number of milling pearls, milling speed, milling time, and temperature. By increasing the drug amount and milling time, the aggregation within the final product would increase. Therefore, it is important to mix an appropriate drug amount for an appropriate amount of time to achieve the desired size of the nanocrystals. Increasing milling pearls and speed can also increase aggregation. However, too many pearls moving too rapidly, would cause weight loading issues in the machining process. Another combination resulting in additional aggregation is an increase in milling speed and milling temperature. Despite differences in processing, the multiple options offer several means to produce nanocrystals with varying properties. The wide range of possible properties is advantageous for its use in potential antiviral applications [34].

One example of nanocrystals being used for antiviral applications occurs in a study conducted by Dostalova's et al., which used Carbon-60

based nanocrystals with a 20 amino acid long protein, H5, and its variants H5N, H5V and H5Y. The nanocrystal itself was structured after the λ -bacteriophage. The original structure of the C-60 nanocrystal yielded very low antiviral activity, but when the fullerene C-60 nanocarriers were enhanced by nitric acid and or trimesic acid, more carboxyl groups were observed on the nanocrystals. Furthermore, there was a more common observation of peptide bonds on the crystals (As discussed earlier, the hydroxyl groups served as building blocks for the nanocrystals in this study, with trimesic acid enhancing the structure for this specific application). The most effective variant of the C-60 nanocrystal application were those with aspartic acid at position 11 replaced by asparagine, valine or tyrosine [35]

5.12. Metal organic frameworks

Metal organic frameworks (MOFs) present several favorable properties in comparison to other nanocarriers. These properties include efficient controlled delivery of retroviral and antitumor drugs (busulfan (Bu), azidothymidine triphosphate (AZT-TP), cidofovir (CDV) and doxorubicin (doxo)) and cytocompatibility. Because MOFs consist of organic and inorganic components, and have high porosity for drug depots, MOFs are often referred to as hybrid porous solids. Furthermore, their metallic makeup is advantageous for bioimaging cancer and viral patients for theranostic and therapeutic purposes. All in all, this presents a positive alternative compared to current options. Many existing materials have poor drug loading capacity, usually of less than 5% of the weight of the vehicle. Also, most carriers favor rapid release mechanisms from the adsorbed drug on the external surface of the delivery system, while MOFs prefer controlled delivery, which is generally more applicable [36]. Overall, despite its novelty, metal organic frameworks' porosity and high drug loading capacity present two unique characteristics that would be favorable, especially for treating viral and cancer patients.

In order to best understand metal organic frameworks, it would be helpful to first understand their structure. Simply put, MOFs are an accumulation of strong bonds between inorganic clusters and organic linkers such as carboxylates. Additionally, in terms of polarity, metal organic frameworks are relatively flexible; the overall structure can be hydrophobic or hydrophilic. This set up yields large pores, which is advantageous for drug delivery and other applications [36]. One of these alternative utilizations include trapping unwanted greenhouse gases from Earth's atmosphere [37]. Furthermore, for medical applications, the pore size is flexible for accommodating different drugs and their required volume dosage. based on the chemical makeup of the specific MOF [36]. MOFs can also be modified to act responsibly to different stimuli, including pH, magnetism, electrostatic responses to ions (ion-responsive), temperature, pressure, light, humidity redox reactions, ATP, H₂S, competitive-binding, liposomes and combinations of these conditions. Furthermore, metal organic frameworks can be made of several types of metals, including Zinc, Iron, Zirconium, Gadolinium, Europium, and Hafnium [38]. Altogether, metal organic frameworks are sometimes referred to as "molecular sponges," because of their ability to encapsulate diverse drugs with different polarities, diameters, and chemical structures [36].

One study conducted by Horcajada et al. looked at porous iron(III)-based metallic organic frameworks. Other studies by Morris et al. and Lin et al. were not appropriate for biomedical applications so they looked for iron-based materials that would fit this criteria better [39,40]. For this purpose, Horcajada et al. used nano scaled iron(III) carboxylate, which was converted to nanoMOFs. They then inserted the aforementioned antiviral and antitumor drugs into the iron(III) carboxylate framework including Bu, AZT-TP, CDV and doxo. Using these nanovessels on mice, there were several key takeaways. Firstly, major degradation of the carrier was observed after just 7 days. Cytotoxicity on mice macrophages was low, and roughly similar to other nanocarriers the same research group had used in the past. Although there were slight

weight increases in the liver, there were eventually no significant differences observed after 3 months. The possibilities for MOFs in humans, for those with viral infections, and especially for cancer, is clear, and undeniably important. Roughly 25% of children diagnosed with cancer are uncured, with current treatment options such as chemotherapy being extraordinarily toxic. Having alternative options for treatment such as through nanoscaled vehicles like MOFs gives scientists hope that these statistics can diminish in the future [36].

5.13. Inorganic-based nanoformulations

There is evidence of inorganic compounds used for medicinal purposes dating back to ancient Greece and Rome, where silver was used as food storage to prevent festering and decomposition. Hippocrates believed silver compounds could prevent infection and promote healing when treating ulcers. Since then, researchers continued to add more metals and inorganic materials to their arsenal of strategy to treat and diagnose various diseases and conditions [41]. Two metal and metal oxide nanoparticles that show high efficacy are gold and silver. The oxides include CuO, TiO₂, CeO₂ and SiO. These metals and oxides have shown to be highly prolific against a wide range of viruses such as influenza, dengue, Hepatitis and HIV-1. The compounds interact with the proteins on the virus surface through Kazimir interactions and Van Der Waal forces. Their similar size and shape to viral particles enables them to inactivate the virus [13]. Metals and oxides with functionalized surfaces (added silane or thiol groups) by virtue of their structure indicate enhanced interaction with biomolecules that affect the internalization of viruses by host cells. Despite proven efficacy, use of inorganic nanoparticles remains limited due to toxicity concerns [1].

5.13.1. Gold nanoparticles

Gold nanoparticles (AuNP's) are colloiddally structured nano-treatments for viruses. Because of its structure, an AuNP possesses special optical properties caused by oscillation of its free electrons. This is useful in imaging functionality of the particles. Research demonstrates that AuNP is capable of reaching and entering the cells that HIV uses as replication reservoirs such as lymphocytes, macrophages, and the micro endothelial cells in the brain. In order to access these areas, researchers attached a thiol group to serve as a linker between the drug Raltegravir and AuNP. When the Raltegravir linked AuNP particles entered infected peripheral blood mononuclear cells (PBMCs), they demonstrated inhibition of HIV replication. When performing the same experiment with a free control AuNP, no antiviral activity was observed [42].

In another instance AuNPs conjugated with siRNA, capable of targeting particular viral genes, were found to have increased stability compared to free siRNA and to reduce viral replication of dengue. The conjugated particles also appeared to inhibit release of infectious dengue virions. siRNAs, due to their small size and anionic property, are typically prone to degradation by serum nucleases and rapid elimination. Conjugation with AuNPs mitigated both consequences [43].

More recently, gold nanoparticles have been studied as a method of causing viral deformation to eliminate functionality. By attaching linkers that mimic heparan sulfate proteoglycans (HSPG) to the surface of AuNPs, the particles could attach to viral ligands and through generation of strong forces, deform them. The particles were nontoxic to cells and effective against not one, but several viruses, including HSV, HPV, RSV, and dengue. It is possible to further stabilize the gold particles by gallic acid. The result is a monodisperse, spherical AuNP of size 7–8 nm. These nanoparticles can selectively inhibit viruses with an improved safety profile compared to drugs on the market at present, such as acyclovir. These nanoparticles are intended to act simply by preventing viral attachment and thus penetration [44].

5.13.2. Silver nanoparticles

Silver nanoparticles (AgNPs) are of particular interest as antivirals because of their intrinsic antimicrobial activity caused by their interac-

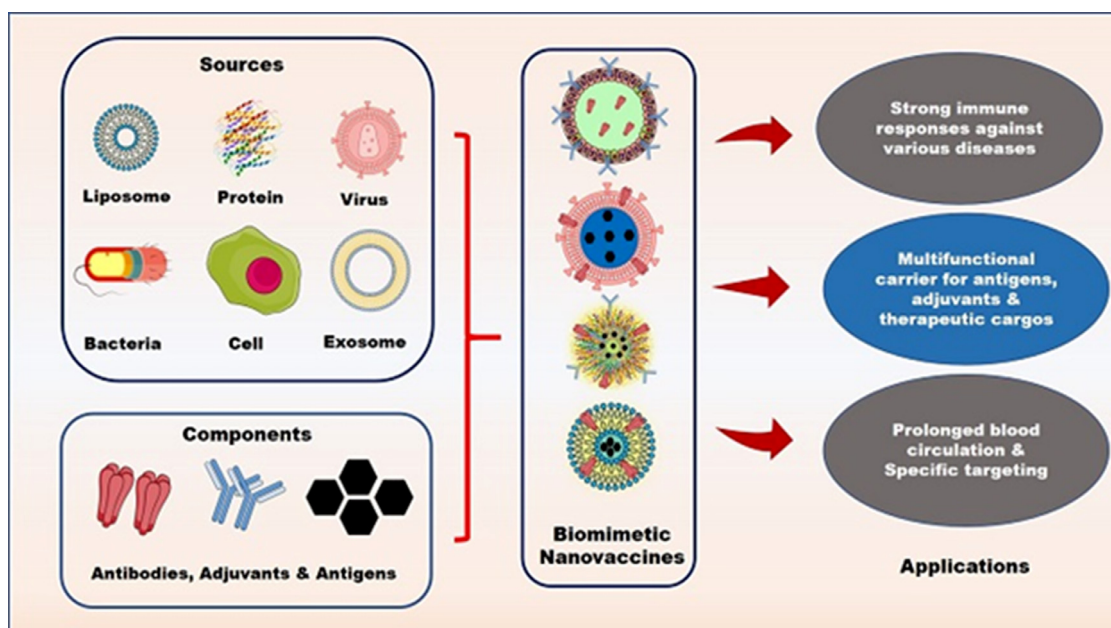


Fig. 7. Depiction of potential combinations of particulate sources and components to create biomimetic nanovaccines and the advantages they bring to a diverse range of applications [2].

tions with the respiratory chain, electron transport chain enzymes, and bacterial DNA. They are extremely small but maintain a massive surface area that enables them to undergo rapid dissolution. Silver nanoparticles have several promising properties that facilitate activity against several viruses such as chemical stability, high conductivity, and localized plasma resonance. Due to the multiplicity of targets they can act upon, they possess less of a chance of initiating development of drug resistance [45].

Research conducted on silver nanoparticles exists primarily with HIV-1 as the focus. Galdiero was the first drug company to study and describe the antiviral activity of AgNPs against HIV-1. The nanoparticles were studied under three surface functions with glycerol as a reducing agent and the AgNPs themselves conjugated with BSA. The hypothesis proposed the interactions between the BSA-conjugated particles and HIV virions to be size dependent. The study found only AgNPs within the range of 1–10 nm to be capable of binding to the virions. Once bound, they were proven to inhibit stages of infection post viral entry through competition with the sulfur and oxygen atoms attached to the thiol or phosphate groups on amino acids or nucleic acids. These interactions facilitated reduction of the reverse transcription rate of HIV-1, the method through which the HIV-1 creates viral copies and further distributes itself through the body [46].

Scientists have also experimented with surface decoration of AgNPs. When silver nanoparticles were coated with oseltamivir, a drug to treat H1N1 which inhibits hemagglutinin activity, the AgNP absorbed with oseltamivir appeared to prevent H1N1 attachment to host cells. The proposed conclusion suggested that the reactive oxygen species (ROS) mediated signaling pathway was interrupted, thus alluding to silver nanoparticles having antibacterial and antifungal characteristics [47].

6. Nanovaccines

Nanovaccines are a subset of vaccines with the engineering goal of attuning host immune response. They are one of the few host-directed options for antiviral therapies. Based on size, shape, functionality and surface composition, nanovaccines can address issues posed by traditional vaccines. Currently, live-attenuated vaccines are limited by the risk of the pathogens reverting to an infectious viral state, virulence. While some vaccines mitigate this risk using inactivated pathogens in-

stead, these induce a weaker immune response. Nanovaccines, due to the aforementioned properties, can overcome these issues and work across a broad-spectrum of immunity [48].

Furthermore, antigens are incorporated into the nanoparticles through encapsulation or conjugation. The nanovaccine protects the integrity of the antigen's basic structure, thus prolonging its presence in the immune cells. The nanostructure allows administration of the vaccines across multiple routes, including intramuscular, subcutaneous, or intranasal. Several nanoparticulate systems have been designed and classified as nanovaccines intending to induce humoral and cellular immunity against viral pathogens. Exploration of biomaterials on the nanoscale for development of these vaccines include phospholipidic, polymeric, inorganic, carbon-based, metallic, and protein based. They are surface modified to carry the vaccines antigens or express the epitopes to target antigen-presenting cells. In terms of metallic systems, sulfide or thiolate gold chemistry have shown promising results regarding successful presentation of antigenic epitopes [48].

In addition, there is some documentation of exploration into multifunctional nanovaccine systems. An oil core-corona architecture capable of loading molecules with a chitosan envelope was assembled with Hepatitis B surface antigens in order to create a single dose vaccine with an elongated period of immunoprotection. The chitosan nanocapsules whose surface charge was positive showed enhanced immune response and sustained effects against hepatitis B. The system was freeze-dried to create a stable vaccine with a long shelf life and recoverable physicochemical properties when thawed and rehydrated for vaccination use (Fig. 7) [1].

7. Surface modifications of nanocarriers

The nanoscale itself improves many material properties and provides plenty of antiviral delivery advantages over conventional scaled delivery systems. However, surface modification is common to further improve nanosystem properties [1]. Two of the most common modifications are charging agents or coatings. Coating ensures that the drug remains in a uniformly dispersed state and to facilitate retention of the nanoparticles' original properties. Charge is modified due to its massive effect on nanoparticulate behavior. Some properties governed by charge are toxicity, compatibility, absorption, and elimination rate. Adding agents of

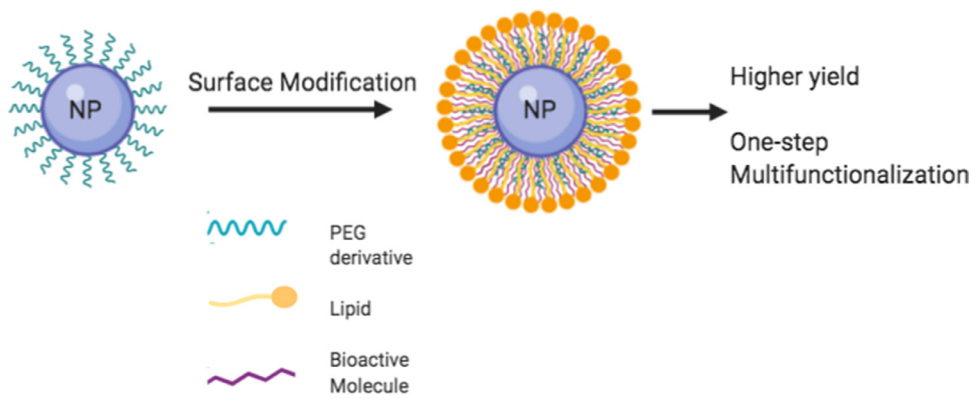


Fig. 8. An example of surface modifications to a generic nanoparticle and its resulting yield increase/multifunctionalization.

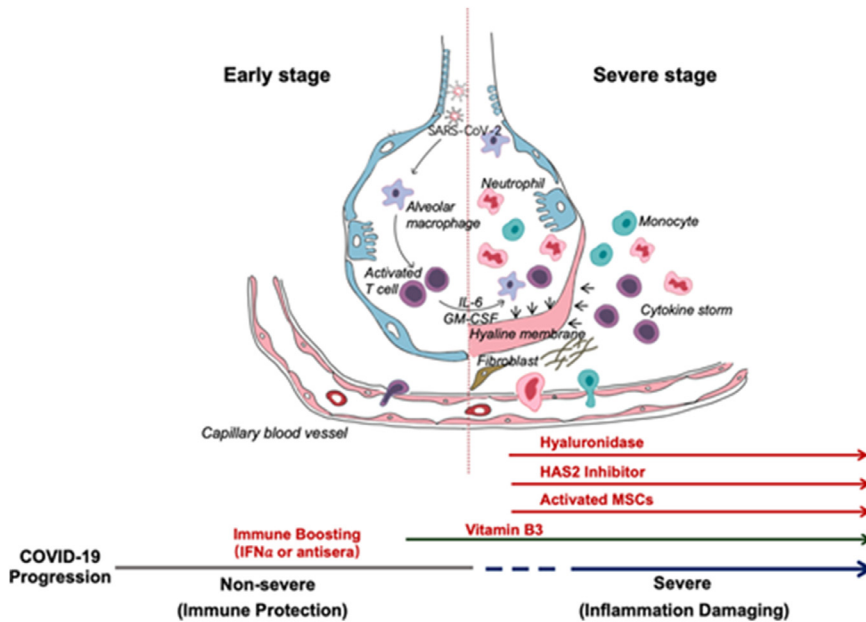


Fig. 9. Demonstrating that early HLA based intervention can act as a potential treatment to prevent COVID-19 infection from progressing from subclinical to clinical infection stage [1].

charge in the form of lipids or polymers can modify the surface's charge. Different nanoformulations function better under different charges. For example, nanoemulsions prefer positive charges because of their effect on loading capacity, and penetration into negatively charged skin. On the other hand, liposomes prefer a negative or neutral charge for its effect on entrapment efficacy and prevention of phagocytosis. When liposomes were negatively charged and loaded with zidovudine, concentration of drug-loaded liposomes accumulated in essential organs such as the spleen was higher, and thus a more effective antiviral therapy (Fig. 8) [49].

Another one of the most important ways that researchers are able to modify the surfaces of their nanocarriers is through chemical treatments. Generally, this method is used to improve the dispersion stability of nanoparticles in liquids. One example of chemical treatments is the adsorption of silane coupling agents. This process is used to improve compatibility between the nanoparticle and other polymeric surfaces. The silane coupling agents are adsorbed to the hydrophilic ends of the outer layer of the nanoparticle, while still interacting with the OH- groups. One example of this is by using 3-methacryloxypropyl trimethoxysilane to replace hydroxyl groups on the surface. This is best illustrated by Figure N below. This yields increased dispersion in these modified nanoparticles. Alternatively, surfaces can also have metal alkoxides and epoxides used for other chemical modifications [50]. Ultimately, chemical treatments for nanoparticles are used for adsorbing chemicals to the outer surface to increase dispersibility.

Aside from chemical modifications of nanoparticles, grafting and ligand exchange can also provide useful surface modifications. Grafting

synthetic polymers to the surface of nanoparticles accomplishes two useful objectives: altering the functionality of surface groups on nanoparticles and changing the physical surface topology. Polymers can be added either by grafting the whole polymer onto the nanoparticle or by grafting the anchoring group and then building the added-on polymer off of it. The latter has generated higher success rates. Some polymers that have shown utility once grafted to nanoparticles are polystyrene, polyacrylamide (PAAM), and methyl methacrylate (MMA). Ligand exchange is an important methodology for providing nanoparticles with more useful ligands on its surface for binding and other purposes. Once synthesized, most nanoparticles have a nanometer thick layer of ligands that effectively act as shields against the movement of free electrons in nanoparticles, which is not favorable. By removing these ligands, the distance between nanoparticles decreases, allowing appropriate charge transport [50]. Ultimately, the ability to alter the surface properties of nanoparticles is wholly important for providing important properties not already provided by the vehicle itself.

8. Future nanosystems for antiviral drug delivery

8.1. Nanobubbles

Nanobubbles are echogenic in nature and consist of an oxygen-containing core that enables them to be loaded with drugs. With attribution to their echogenic nature, they can be used in site-specific delivery of the loaded drugs using ultrasound technology. It is possible for the core to contain other gases such as perfluoropentane and

decafluoropentane. The shell of nanobubbles is a lipid polymer based coupled with a surfactant. This provides the nanobubble with stability, ideal half-life, and idealized acoustic parameters for inducing drug release at the target site. Using ultrasound as a means for active targeting is minimally invasive and more stable than some other active targeting methods. Improved stability is also achieved. Moreover, the nanobubbles, like other nanosystems can be surface modified for theragnostic (multifunctional diagnosis and treatment). They have such a versatile structure that they can be incorporated into a variety of molecules and thus can act as methods of diagnosis, treatment, and infection prevention. Again, due to their echogenic nature they possess a unique and intriguing application of real-time ultrasound visualization of the target area and drug [51].

8.2. Nanofibers

These nanoscaled fibers are produced using the electrospinning technique. They are spun from polymers such as polyvinyl alcohol, chitosan, polyethylene oxide and cellulite acetate. The drug itself can be uniquely incorporated into the nanofiber in either its pure form or nanoparticulate form. As of now, the initial burst release of the drug remains a concern but adopting a core-sheath design minimizes this risk [52].

Unique properties attributed to structure include a large surface area, high porosity while maintaining small pore size, and high mechanical strength. Like many other nanotechnologies, nanofibers can be surface modified. Some experimentation with nanofibers has already achieved controlled release of hydrophilic anti-HIV drugs, including raltegravir, and maraviroc. The fibers were spun and blended with biodegradable polyesters PCL and PLGA. Variation of the polymer ratios tuned and controlled the ideal sustained release [53].

8.3. Nanodiamonds

Nanodiamonds are a nontoxic carbon-based nanomaterial. A stable sp³ carbon composes the core while the surfaces are faceted and capable of co-coordination with surrounding water molecules. Thus, they are highly effective at solubilizing water-insoluble drugs. Production occurs at high temperature and high pressure, or through the detonation method. They possess desirable properties such as structural stability, non-toxicity, increased bioavailability, biocompatibility, loading capacity, stability, and elongated circulation time. As with many others, they can be surface modified for site-specific delivery and further functionalized with growth factors [54].

8.4. Nanotraps

Nanotraps are nano-scaled homogenous hydrogels that are used to capture viruses. These nanotraps are characterized by their charged, high affinity aromatic cores that are surrounded by a polymerized shell. The hydrogel derivative and the outer charges promote hydrophobic and electrostatic interactions respectively. The outer shell essentially attracts the virus, while the inner hydrogel structure keeps the virus within. Additionally, nanotraps are easily chemically and physically altered for different purposes. Nanotraps generally capture the virus via the sieving shell and keep them inside the expansive hydrogel core. Nanotraps don't necessarily degrade the virus, but rather hold it inside the hydrophobic interior. In fact, the nanotraps actually protect the captured virus and viral proteins from proteases. Because it captures its target rather than degrade it, they have been used to capture HIV-1 viruses for further research [55].

One nanotrap that was used to capture HIV-1 from patients had a hydrogel core made of Cibacron Blue, and a polymer shell made of N-isopropylacrylamide, N,N -methylenebis- acrylamide, allylamine, methacrylate and vinylsulfonic acid. Other materials that are often used to create nanotraps are acrylic acid, Acid Black 48 and pigment red. Aside from HIV, nanotraps have been used for the capture of RSV, rift

valley fever virus (RVFV), venezuelan equine encephalitis virus (VEEV), and intact foot-and-mouth disease virus (FMDV). This works both as a treatment and a means of capturing viruses that can be used to create vaccines. Other applications for nanotraps include the purification of viruses such as FMDV. Furthermore, nanotrap particles can specify the molecular size of the particular virus, which increases detection and capture efficacy. In addition to its hydrogel properties, magnetic properties have also been developed to keep specific viruses at particular temperatures for effective storage, including VEEV, which favors temperatures of around 40 °C. Another application for nanotraps is for the treatment of severe sepsis using telodendrimer nanotraps (TDNTs). These TDNTs are used to capture biological molecules associated with the sepsis through multivalent, hybrid and synergistic interactions. One study showed that this specific application of nanotraps in conjunction with the typical antibiotic treatment permits a 100% survival rate in septic mice subjects because of the general control over the hyperinflammation. Unlike other treatments discussed throughout this paper, nanotraps are very effective for both the diagnosis of viral illnesses and assisting in capturing these viruses and their proteins for further research [1].

8.5. Nanorobots

Nanorobots are nano-sized devices that consist of inorganic, polymeric and biomimetic materials that can be used to remotely travel through the bloodstream. This methodology can be used for the diagnosis and treatment of cancer and diabetes, along with neurological and cardiovascular disorders. Being that these miniature machines are controlled, they can perform multiple tasks for researchers to deliver drugs to different areas of the body through the bloodstream. In terms of their structure, nanorobots are essentially miniature circuits. They include a power source, sensors, actuators, minicomputers, pumps, structural support, compartments for the drug being delivered, and cameras to assist the doctors and researchers with steering and precision locating. With these components, these robots can actuate, propulse, sense, signal and self-replicate in their goal of navigating the body for diagnosis and or treatment. Although nanorobots have not been used for antiviral delivery and treatment yet, it is hard to see a future where this is not possible, especially considering the recent advent of nanochips (for storing instructions for tasks to be completed), nanobiosensors (to send signals to the nanochip), nanotubes (for probing specific nuclei) and nanocontainers (to store DNase and RNase for attacking viruses). Overall, nanorobots present themselves as very intriguing methods for the potential future of antiviral drug delivery [1].

9. COVID-19

Despite the threat of COVID-19 looming around the corner since the final months of 2019, it took until March 11th, 2020 for the World Health Organization (WHO) to declare the outbreak as a global pandemic [56]. Initially, the WHO and CDC emphasized the danger that the newly spread coronavirus posed to elderly individuals as well as those with pre-existing conditions [57]. Despite the clear warnings made by leaders within the public health and medical communities, many countries did not act swiftly, directly contributing to lengthening the pandemic. The WHO Director-General, Dr. Tedros Adhanom Ghebreyesus had the following to say regarding the situation: “[The WHO is] deeply concerned both by the alarming levels of spread and severity and by the alarming levels of inaction...We should double down...We should be more aggressive” [56].

9.1. Initial spread and international response

The first known cases of COVID-19 occurred in December 2019 in Wuhan, Hubei in China, as a large cluster of individuals presented symptoms of severe pneumonia. Some of the individuals within the first group

of coronavirus patients were linked to a local wet market. Upon the initial spread of the virus, doctors deduced that the disease was a novel strain of the coronavirus, related closely to SARS and MERS. By January 30th, 2020, the WHO declared the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern. On January 31st, the U.S. Centers for Disease Control (CDC) announced that United States citizens travelling from Hubei, China would be required to quarantine for 2 weeks. However, as the ongoing pandemic within the United States has shown, the virus had already gotten here both from China and other countries [56].

Upon initial research into the disease, scientists found that even asymptomatic patients were potentially capable of spreading the illness. One German businessman showed severe symptoms, and it was determined this patient's business partner from Shanghai was likely the one who transmitted the disease to him. She tested positive upon her return to China, but she showed no symptoms pointing towards possible contagiousness in an incubation period or from asymptomatic patients. Initial studies showed that the average incubation period was roughly 6.4 days, with a 95% confidence interval of 5.6–7.7 days. Due to this development, health authorities needed to treat their response to this pandemic differently than other possible outbreaks. This led to the emphasis on active monitoring, which essentially evolved into what is now commonly known as contact tracing [56].

9.2. Potential treatment

Because no vaccine has been provided for the common public and likely won't be readily available until the end of 2020 or the beginning of 2021, it is truly crucial for treatments to be found in the meantime. Despite the novelty of the coronavirus, there are several promising treatments that utilize the different types of nanoparticles outlined throughout this paper. The importance of this is strongly supported by the simple fact that many of the current treatments are for fighting the symptoms, rather than the virus itself. That is why it is imperative to understand the process by which SARS-CoV-2 infects the human body. The SARS-CoV-2 uses angiotensin converting enzyme II (ACE2) in a "Lock and Key" mechanism that allows the virus access to cells that have ACE2's corresponding lock. These sites can be found throughout the body, but especially in the lungs, hearts and arteries [58]. This process emphasizes the focus on finding a treatment that could potentially inhibit this "Lock and Key" process altogether.

Some potential treatments include the following: inhibitors of TMPRSS2 and ACE2, which are associated with the treatment of malaria; inhibitors of RdRp; inhibitors of associated proteases; inhibitors of virus-cell membrane interactions; and phytochemicals. The specific drugs studied to act as inhibitors of cell entry can be separated into two groups: those that inhibit TMPRSS2 serine protease, and those that inhibit angiotensin-converting enzyme 2 (ACE2). Overall, camostat mesilate (Foipan), and nafamostat mesilate (Buipel) are promising inhibitors of TMPRSS2, while chloroquine phosphate, hydroxychloroquine, cepharanthine, selamectin, and mefloquine hydrochloride show potential for the inhibition of ACE2. Aside from looking for ACE2 and TMPRSS2 inhibitors, it is important to note that SARS-CoV-2 utilizes protein kinase 1 (AAK1) as the main tool to regulate or promote endocytosis in infected cells. There are certain drugs that can suppress AAK1, but they are generally oncological, and could cause undesirable side effects. One of these potential drugs is the janus kinase inhibitor (JAK) [58].

In addition to inhibiting the proteases associated with the bonding of the virus and the cell, inhibitors for viral replication, membrane fusion, and viral assembly are also relevant for initial treatment. Remdesivir has shown antiviral activity against single-stranded RNA viruses by inhibiting successful viral RNA synthesis. However, it is most effective early in incubation. Lopinavir and ritonavir are relevant treatments by blocking viral assembly through active mutation of valine amino acids, while umifenovir prevents cell entry by actively blocking membrane fusion. This membrane fusion is blocked by inhibiting clathrin-mediated

endocytosis. Favipiravir is responsible for inhibiting RNA polymerase (RdRp) for other known RNA viruses, which in turn causes devastating mutations during replication. 3Clpro protease is an essential protease of SARS-CoV-2, so inhibitors of this protease such as ebsele are potentially useful for treatment as well. Phytochemicals have also been shown to be promising in the treatment of other RNA-based viruses, as they interfere with NLRP3 inflammasome signaling. Some examples of potential phytochemicals used for this purpose are luteolin, myricetin, apigenin, quercetin, kaempferol, baicalin and wogonoside. Overall, despite vaccines still being in development, there are numerous potential treatments that can and should be looked into in the meantime [59]. Despite these treatments, positive COVID-19 cases have continued to rise alongside the mortality numbers. That is why looking upon new horizons, like nanoparticles, is a particularly promising direction.

9.3. Nanotechnology applications

Before discussing the specific nanoparticles that could be used for this purpose, it is important to discuss the administration first. For the purposes of this paper, we will discuss intranasal delivery, specifically mucosal administration. This methodology is possible because of the favorable conditions presented by nanoparticles, as outlined countless in this paper: low toxicity, size modifications, charge modifications and chemical flexibility. On the other hand, mucosal administration presents several favorable conditions for the nanoparticles themselves. For one, it prevents unwanted enzyme degradation. This in turn can extend drug release time, allows delivery alongside adjuvants, can maintain a steady concentration of the drugs being delivered and makes it infinitely easier for targeted delivery. Logistically, it is also noninvasive, simple, and cheap. In order for this methodology to have maximized efficacy, the preferred conditions of the nanoparticle itself must be met. These include a size range of 100–200 nm, being positively charged, hydrophobic, and containing therapeutic moieties on the surface [60].

The first type of nanoparticle that can be used for treating SARS-CoV-2 intranasally are organic nanoparticles, including lipids, polymers and dendrimers. Lipids are convenient for this purpose because of its characteristic biocompatibility. Liposomes specifically are useful because of their spherical, phospholipid structure. The inner hydrophilic core, and other hydrophobic core is useful for storing and administering many drugs. Furthermore, liposomes are cationic, which helps its compatibility with the negatively charged mucus. Polymer-based nanoparticles are useful because of their flexible synthesis conditions, which can yield linear, branched or 3D. This makes the nanoparticle shape malleable for tuning purposes. Chitosan is one example of a possibly useful polymer for drug administration, especially due to its biodegradability. Lastly, dendrimers, with their radial symmetry, monodispersity and homogeneity, make it easy for the addition of functional groups. This is helpful for protecting the hydrophobic agents that may be stored in the nano-scaled drug depot [58].

Inorganic nanoparticles have their own strengths and weaknesses for treating coronavirus patients. Gold or other metallic materials are favorable because their magnetism makes it easy for imaging in vivo. However, more studies must be conducted to ensure appropriate biocompatibility. Two of the most commonly used inorganic materials are gold and silver. Gold-based treatments are considered a major possibility for theranostic purposes, because of their adaptability, diffusibility into important organs like lymph nodes, and their high atomic number for CT imaging [58]. On the other hand, a study conducted by Oron Zachar looked to test the minimal inhibitory concentration (MIC) of silver nanoparticles targeted to the respiratory system. This was looked at to be an early viral stage home treatment while also an option for preventing ventilator associated pneumonia at ICUs. Although efficacy in humans wasn't tested, the group was able to create silver particles of 5 nm in diameter that would appropriately be able to penetrate the bronchial tree and alveoli [61].

Virus-like nanoparticles (VLNP) are the last, but also most intriguing, group of nanocarriers for antiviral treatment of COVID-19. VLNPs are sphere shaped, with a diameter range of 20–200 nm, which is comparable to the 125 nm size of SARS-CoV-2. These VLNPs are made of proteins from real viral capsids but contain no genetic material. By acting as a copycat with the appropriate antigens attached, they can trigger an immune response, while successfully avoiding typical enzymatic degradation associated with nucleic acids. Furthermore, the small size can penetrate some cellular nuclei, and can subsequently be imaged with MRI or PET scans. One example of a popular VLNP used for antiviral drug delivery is known as Self Assembling Protein Nanoparticles (SAPNs), which are well organized with non-covalent bonding [58].

Using these different nanomaterials, there are several means of which to treat viral infections, including enhanced drug delivery, siRNA, inhibition, and early prevention. One example of enhanced drug delivery would be to nano formulate drugs like Sunitinib and Erlotinib for blocking AAK1. However, the unwanted side effects would be minimized because the targeting would reduce the dosage required, making it less dangerous. siRNA can be delivered using a multitude of materials, including lipids, inorganic and polymeric nanoparticles. This siRNA can potentially be used for RNA interference on SARS-CoV-2. Peptide inhibitors have also been used to prevent cellular entry by preventing the virus from latching onto cells to begin with. For comparison, SARS-CoV-2 has the same Spike Protein (S protein) as MERS-CoV, which also contains S1 and S2 units that play roles in binding to the cellular membrane. This is accomplished at the dipeptidyl peptidase 4 (DPP4) receptor. However, HR1 peptides can inhibit this process, while reinforcing these peptide-based nanomaterials with gold nanorods increase the efficacy of the method tenfold. Gold nanoparticles and Carbon Quantum Dots (CQDs) are alternatives for viral entry prevention [58]. Overall, nanomaterials that are effective for the treatment of other viruses could certainly be altered and specified for potential use against the coronavirus, and other novel viruses in the future.

As the world draws nearer and nearer to a potential vaccine for the COVID-19 virus, it has become clear that nanotechnology can play an important role in both treatment, and vaccine development. Without an antiviral, there are methods in which the virus can be targeted to prevent membrane fusion, replication and viral assembly with different drugs and antivirals used for other related RNA viruses as outlined above. One mRNA-based vaccine using LNPs is in clinical trials in the United States. Although there is current research being conducted, it is important to look towards the future as well to see how nanotechnology can potentially be used during, and in preparation for the next pandemic [62].

10. Conclusion

Overall, we hoped to elucidate the propitiousness of nanotechnology in the medical field. We particularly focused on the use of nanoparticulate carriers as antiviral drug delivery systems. There are a wide variety of carriers from lipid-based to inorganic-based, and each of these have unique properties that can be further explored to improve many of the issues associated with current drug delivery systems. Through their natural attributes like small size, and high surface area to volume ratio, as well as the surface modifications we can make, nanoparticles can overcome common barriers such as bioavailability, site-specific targeting, and high dose requirements. In doing so, they may lead to development of not only more potent, effective antivirals, but also higher rates of patient compliance, reduced cases of drug resistance, and lower cost.

Although not a new concept, the in-depth study of nanomedicine is a field in its infancy. One of the major issues that is still not fully understood is the potential for nanotoxicity. The scientific community would need to ensure that the risk-benefit favors the beneficial side of treatment, as in many cases viruses are not fatal and less time dependent than say cancer. Furthermore, cost analysis and the production scala-

bility need to be considered before nanoparticles can be deemed the primary antiviral drug delivery mode.

Moreover, attributed to their unique physical properties, there is potential for further study of nanocarriers to be multifunctionalized for use in theranostics. This means that not only will the nanoparticles act as drug delivery vehicles, but also as diagnostic tools. As so many viral infections are subclinical, it would be highly beneficial in stopping the spread of the virus through early detection and early mitigation of symptoms to limit the severity of infection.

Within this paper, we have discussed several promising potential nanoscale treatments for SARS-CoV-2. These treatments include organic options, including lipids, polymers and dendrimers, which are favorable due to their biocompatibility and biodegradability. On the other hand, inorganic nanoparticles made of gold and silver have true potential for theranostic imaging purposes, while also being suitable for the inhibition of the “Lock and Key” system. Despite questions regarding the biocompatibility of these options, it is reasonable to believe that a combination of these substances in the form of metal organic frameworks could yield high efficacy and utility. Lastly, virus-like nanoparticles also show promise for triggering immune responses with decoy antigens. Options for treatment in the nanosized vehicles discussed in this paper would certainly include enhanced drug delivery, RNA interference, and viral inhibition.

Overall, we cannot overlook the importance of the future of nanotechnological applications for viral treatment, especially in light of recent global events. The COVID-19 pandemic has proven that much of the world is generally united on one front: unpreparedness for viral outbreaks. This lack of preparation magnified the importance of having prepared researchers to engineer treatments, especially in fields best suited to the modernization of detection and vaccination. Nanotechnology is most certainly one field that should be expanded upon in this regard, especially due to the diverse set of biomaterials that it has at its disposal. It cannot be argued that the field of nanomedicine is rapidly expanding. We hope through reviewing the wide range of potential carriers and pointing toward the issues it can solve, to have encouraged further need for research into the use of nanoparticulate carriers as antiviral drug delivery vehicles. Even though nanoparticle-based antiviral drug delivery is a relatively modern concept, if it is given appropriate funding and attention, it could dominate the medical world now, and for years in the future.

Disclosure

This manuscript was written to serve as a term paper for BME 353, introduction to biomaterials, at Stony Brook University under the guidance of SUNY Empire Innovation associate professor Dr. Donghui Zhu. Publication was pursued after completion of the class. As per university policy Dr. Zhu serves as the corresponding author on this manuscript.

Declaration of Competing Interest

None.

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