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Nanotechnology used in treatment of viral disorder

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Abstract
Infectious diseases are the leading cause of mortality universal, with viruses in particular making global effect on healthcare and socioeconomic development. In addition, the rapid development of drug conflict to currently available therapies and adverse side effects due to continued use is a serious public health concern. The development of unique treatment strategies is therefore required. The interaction of nanostructures with microorganisms is fast-revolutionizing the biomedical field by offering advantages in both diagnostic and therapeutic applications. Nanoparticles offer unique physical properties that have associated benefits for drug delivery. These are mainly due to the particle size, large surface area to volume, tunable surface charge of the particle with the possibility of encapsulation, and large drug payloads that can be accommodated. These properties, which are unlike bulk materials of the same compositions, make nanoparticulate drug delivery systems ideal nominees to explore in order to succeed and/or increase therapeutic effects. This review presents a broad overview of the application of nanosized materials for the treatment of common viral infections.

Keywords: Nanotechnology, viral infection, Vaccine, HIV, Antiviral nanotherapeutics

Introduction
Infectious disease agents such as bacteria, viruses, fungi [1] and parasites account for approximately 15 million deaths worldwide, with acute respiratory infections and human immunodeficiency virus (HIV) being the leading causes. Viral infections alone pose significant global health challenges by affecting millions of people worldwide, with a negative impact on both health and socioeconomic development. Efficient treatment of viral infection is hindered by the development of drug resistance, especially those associated with HIV and influenza. This phenomenon constitutes a public health threat, which includes increased morbidity and mortality, added costs associated with the use of more expensive drugs and a greater burden on public health systems [1].
Nanotechnology refers to the development or application of particles with dimension(s) that fall into the nanometer range (10^{-9} or one billionth of a meter). The interaction between nanoscience and biological systems is known as 'nanobiotechnology'. While the associated area known as 'nanomedicine' deals with the application of nanostructured materials to diagnose, treat and prevent diseases.

History
The first Nano systems applied in medicine were introduced to increase the efficacy of current, yet dose-limiting and poorly bioavailable drugs. Currently, nanoparticles are known to exert their antiviral activities by various mechanisms. First, the unique properties of nanoparticles such as

1. Small particle size (which can facilitate drug delivery into anatomically privileged sites),
2. Large surface area to volume ratios (which ensures that large drug payloads can be accommodated),
3. Tunable surface charge (to facilitate cellular entry across the negatively charged cellular membrane), make nanoparticles attractive tools for viral treatment.
   Second, it has been demonstrated that nanoparticles can contain biomimetic properties, which result in intrinsic antiviral properties. Popular examples of these include silver nanoparticles and dendrimers.

Third, the possibility of drug encapsulation, functionalization by the formation of stable structures, or modifications (with polymers such as poly (ethylene glycol) (PEG)) can all lead to optimized drug dosing and improved delivery by increasing stability and drug retention times.

Finally, it is believed that drug delivery can be vastly improved by engineering nanoparticles with targeting moieties to increase specificity to desired cell types, target tissues or sub-cellular compartments. A condensed summary of the mechanistic approaches to engineer nanoparticles with improved treatment benefits is shown in the schematic in Figure 1.

Scope and objectives

Certain challenges exist for the treatment and subsequent eradication of viruses in the infected host. Example is the establishment of reservoirs in cellular and anatomically privileged sites such as the blood-brain barrier (BBB) and blood-testis barrier [4]. This leads to low-level replication in these compartments, which are inaccessible to conventional therapeutics. Nano particulate drug carriers are, however, able to traverse these membranes and are therefore promising tools to be investigated for circumventing this obstacle [7]. Other challenges in viral treatment include the use of RNA interference (RNAi) technology – a popular molecular approach for the treatment of many infectious diseases. The inability of RNA to cross the cell membrane, due to the large molecular weight and anionic charge, rapid renal clearance, uptake by phagocytes, and toxicity due to stimulated immune response, all present limitations which prohibits their clinical utility. The incorporation of siRNA onto Nano carriers, however, can also overcome this limitation to achieve successful inhibition of viral replication. This review will provide an overview of the most recent (past 5 years) and relevant literature, which describes the application of nanotechnology for the treatment of common viral infections. Examples of Nano systems with applications in both drug and vaccine delivery for prevention of these viral infections are also reviewed. Finally, important considerations for nanoparticle antigenicity as well as the requirements for the design of nanomaterial's, which are unique to viruses, are discussed [1].

Examples of biocompatible systems

A Nano pharmaceutical refers to any nanomaterial with therapeutic potential, for example, dendrimers, liposomes, micelles and Nano capsules. These can function as therapeutic agents, whereby the drug is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles can have various shapes and chemical compositions and can be classified according to the way drugs are delivered or by the characteristics of the matrix of which it is composed. Here, we describe the most common types of nanocarriers (Figure 2) that are used for drug delivery, based on their composition.

Types of nanoparticles

Organic nanoparticles

Organic nanoparticles are the most extensively researched type of nanoparticle for drug delivery and the most widely approved system for therapeutic use in humans [2]. The most common types of organic nanoparticles are presented as follows.

Polymeric nanoparticles

Polymeric nanoparticles are colloidal solids with sizes ranging from 10 to 1000 nm. The small size can facilitate capillary penetration and uptake by cells resulting in increased concentrations at target sites [3]. Polymers approved by the World Health Organization (WHO) and the Food and Drug Administration (FDA) for use in medicine and pharmaceuticals include polylactides (PLA), polyglycolides (PGA) and poly (lactide-co-glycolides) (PLGA). Poly (D, L-lactide-co-glycolide) (PLG) and PLGA-based nanoparticles are most widely used due to their superior biocompatibility and biodegradability profiles. Surface modifications with hydrophilic polymers such as PEG are essential to reduce non-specific interactions with serum proteins, decrease susceptibility to opsonizationand to defer uptake by phagocytosis, thereby prolonging the drug half-life and further altering the biodistribution and pharmacokinetic profile of the drug, and has thus been considered as the 'gold-standard' of cloaking agent systems. Polymeric nanoparticles can be classified as nanocapsules or nanospheres.

Nano capsules

Nano capsules are hollow spheres, in which the drug is confined to an inner cavity, surrounded by a polymer coating. The size can range from 50 to 300 nm, and they are characterized by their low density and high loading capacities [3].

An example of the use of Nano capsules in enhancing drug distribution is described; limited antiviral distribution to brain tissue may be due to the permeability glycoprotein (P-gp) efflux transporter. Solutol® HS15 is an excipient that is able to inhibit P-gp, thereby improving drug distribution across the BBB. Results from this study demonstrated that Solutol ® HS15 Nano capsules loaded with the HIV protease inhibitor, indinavir, showed significantly increased uptake in the brain and testes of mice, compared to control mice where only indinavir solution was administered [4].

Nano spheres

These are matrix systems where the drug is physically or uniformly dispersed, with sizes ranging from 100 to 200 nm in diameter. Several research studies have been done using nanospheres for the treatment of hepatitis B virus (HBV), herpes simplex virus (HSV), and influenza, while comprehensive review articles on the application of these agents in viral treatment are also available [5].

Liposomes

Liposomes are spherical carriers ranging from 20 to 30 nm in size. They are composed of a phospholipid bilayer (which can mimic cell membranes and directly fuse with microbial membranes), containing an aqueous core. Hydrophilic and lipophilic drugs (or other biologically active compounds) can be incorporated into the inner aqueous cavity or the phospholipid bilayer, respectively. Additional advantages of liposomes are that they are relatively non-toxic and biodegradable. Liposomal formulations have been extensively studied in vaccine studies due to their ability to act as immunological adjuvants [6].

Micelles

Micelles range in size from 10 to 100 nm. These are composed of an inner hydrophobic core (which can incorporate poorly water soluble drugs) and surrounded by an outer hydrophilic polymer (such as PEG, which can increase circulation time and consequently improve accumulation) [3]. Examples of these include polymeric micelles, which have attracted much attention as drug

delivery agents with significant therapeutic potential. Drug encapsulation with polymeric micelles is one of the most attractive nanotechnologies used to improve both the water solubility and stability of otherwise technologically limited (poorly water soluble and unstable) drugs. An additional advantage of using micelles in therapeutics is that they display a slower rate of dissociation, thereby enabling a longer drug retention time, and eventually a higher accumulation of the drug at the target site [7].

Dendrimers

Dendrimers are symmetrical, macromolecular, and hyper-branched structures radiating from a central core via connectors and branching units, where interaction with its target environment is controlled by the terminal groups.8 These are globular in nature and comprised of three distinct domains (central core, branches, and terminal functional groups). They have increased functionality because they can encapsulate several chemical moieties, interior layers and have the ability to display multiple surface groups (multivalent surface) [7, 8].

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) represent an alternative drug delivery system to the conventional colloidal nanoparticles, described above. The use of SLNs also aims to combine the advantages of conventional Nano carriers, while avoiding some of their limitations. For example, large-scale production of polymeric nanoparticles is a major challenge, which limits their utility in drug delivery, whereas the production of SLNs can be achieved in both cost-effective and relatively simple ways (e.g. by high pressure homogenization and micro emulsion techniques). Additional advantages of using SLNs include increased stability, safety and availability, and decreased toxicity, with improved drug-release profiles, compared to synthetic polymer nanoparticles [9].

Inorganic nanoparticles

Metallic nanoparticles can be smaller than organic nanoparticles, ranging between 1 nm and 100 nm in size, while their loading efficacy is much higher [7]. There are two main approaches for the synthesis of metallic nanoparticles: the 'bottom-up' (or self-assembly) approach refers to the construction of the nanoparticle, level by level (e.g. atom by atom or cluster by cluster), and the 'top-down' approach uses chemical or physical methods to reduce the inorganic material to its Nano sized form. The reaction conditions (pH, temperature, time, or concentration) can be used to modify the nanoparticle characteristics (size and shape), while the choice of reducing agent can influence properties such as loading capacity, release, and aggregation profiles [2].

Gold nanoparticles

Gold nanoparticles (GNPs) are widely researched as nano carriers due to their excellent conductivity, flexibility of surface modification, biocompatibility, and simplistic preparation methods. Other advantages afforded by their unique physical and chemical properties include the gold core (which is inert and non-toxic), photophysical properties (which can facilitate efficient drug release at remote sites), and versatility of functionalization via thiol linkages. There are basic GNP preparation methods which exist and can produce nanoparticles of varying diameters [10, 11].

Silver nanoparticles

Silver nanoparticles are the most effective of the metallic nanoparticles against bacteria, viruses and other eukaryotic microorganisms, particularly due to the inherent inhibitory and bactericidal potential of silver, but also because of their good conductivity, catalytic properties, and chemical stability. The key mechanisms of action of silver nanoparticles are the release of silver ions (which enhances antimicrobial activity), cell membrane disruption, and DNA damage. 91 The reader is referred to a detailed review on the application of silver nanoparticles as virucidal agents [12].

Antiviral nano therapeutics

HIV

A cure or vaccine for HIV/AIDS remains elusive. Treatment is based on the use of drugs that target the various stages in the life cycle of the virus. The current antiretroviral (ARV) armamentarium includes six classes of drugs, that is, nucleoside/nucleotide reverse transcriptase inhibitors (N (t) RTIs), non-nucleoside inhibitors (NNRTIs), protease inhibitors (PIs), entry/fusion inhibitors (FIs), CCR5 antagonists, and integrase inhibitors [13].

The combination of three or more drugs, known as highly active ARV therapy (HAART) has significantly improved the expectancy and quality of life of HIV-infected individuals. This type of therapy, however, is not devoid of unwanted occurrences; suboptimal adherence, heavy pill burdens, toxicity and other negative side effects, are all limitations of currently available therapeutics. Moreover, the chronic nature of HIV/AIDS infection requires that life-long treatment be taken, which can result in the development of drug resistance. It is therefore essential that novel methods to enhance the inhibition of HIV infection be investigated and developed.

Nanotechnology-based drug systems for HIV treatment represent an important option that requires ongoing investigation. Modern drug design, which can incorporate ARV drug delivery with nano systems can decrease the dosage requirements and toxic side effects associated with current heavy pill burdens (which reduces the possibility of drug resistance), thereby improving the safety and efficacy profiles of the drug [7].

Different reviews have been published that focus specifically on HIV/AIDS vaccine developmentand delivery of siRNA for the treatment of HIV. The reader is also referred to comprehensive accounts on conventional methods for HIV treatment and the recent advances using different types of nanoformulations with their respective applications in HIV treatment [14].

Jaramillo-Ruiz *et al*., demonstrated for the first time that carbosilane dendrimers can be used for the prevention of Treg cell infection with HIV, *in vitro*. The negative phenotypic effects and decreased functionality of these cells due to HIV infection were also decreased with the application of these dendrimers. In addition, high biocompatibility and significant reduction in p24 antigen production was observed in cell culture and intracellularly [15].

In a study by Parboosing *et al*., [16] RNA decoys in the form of a 16-mer oligoribonucleotide originating from the stem loop 3 of the HIV packaging signal, were attached to

dendrimers in an effort to disrupt the packaging process of the HIV life cycle. The results of this study demonstrated efficient delivery into lymphocytes and modest cyto protective effect against HIV infection [16].

Jayant *et al*., [17] demonstrated that an ARV (tenofovir) and an investigational latency-reversing drug (vorinostat) can be co-encapsulated on ultrasmall (10 ± 3 nm) iron oxide nanoparticles. This research achieved a sustained drug release period (increased by 30%) showing absolute drug release profiles over a 5-day period with simultaneous activation of latent HIV in cultured human astrocytes. Improved transmigration ability across the BBB and *in vitro* antiviral efficacy was also demonstrated [17].

HBV

HBV causes inflammation of the liver and is the cause of chronic infection in approximately 240 million people. Complications of HBV infection include cirrhosis and liver cancer and accounts for more than 780,000 deaths per year. Current anti-HBV nano-therapy includes interferon (IFN)-α, pegylated IFN (Pegasys®), lamivudine (Epivir®), adefovir (Hepsera®), entecavir (Baraclude®), telvivudine (Tyzeka®), and tenofovir (Viread®). Limitations of anti-HBV treatment include high costs, undesirable side effects, the risk of liver failure during hepatic flares, and development of drug resistance.

New developments for HBV treatment using nanotechnology are being investigated. In an *in vitro* study done by Wang *et al*., different types of cationic nanoparticles composed of biodegradable polymers were prepared by nanoprecipitation and solvent evaporation methods. These nanoparticles were evaluated for their transfection efficiencies in delivering siRNA and DNA to finally achieve inhibition of hepatitis B surface antigen (HBsAg) production. The results demonstrated that methoxy poly (ethyleneglycol)–poly (lactide) (mPEG–PLA) nanoparticles, containing a polyethyleneimine (PEI) layer, achieved the highest ant-HBV effect, and that successful delivery of siRNA is dependent on both size and surface charge.18

Hepatitis C virus

Hepatitis C virus (HCV) infects approximately 130–150 million people globally, with progression to liver cirrhosis or liver cancer being a common occurrence. Approximately 500,000 people die each year as a result of HCV-related liver disease. Standard nano-treatment for HCV infection is based on the use of PEGylated IFN and ribavirin.

Peginterferon α-2a (Pegasys®) was approved by the FDA for the treatment of HCV in 2002, while Peginterferon α-2b (PegIntron ®) was available in 2001. The latter drug has a molecular mass of 31 kDa showing superior results in clinical studies (versus the un-PEGylated form IFN-α2b of 19 kDa).

It has been demonstrated that IFN-α can be efficiently coupled to GNPs (physical binding), complexed with hyaluronic acid (HA) (via a thiolated interaction) for the target-specific and long-acting delivery in mouse models. These nano-complexes remained in the liver for 7 days post-injection (when compared to native IFN-α and PEG-Intron), thus offering great potential for the enhanced and prolonged treatment of HCV infection [19].

In a separate studycross-linked polymeric micelles (CLPM) were used to target HCV, *in vitro*. The micelles were loaded with the recently identified potent anti-HCV compound, camptothecin (CPT), which is also associated with limitations such as poor water solubility and chemical instability. The CLPMs used in this study enabled the formation of suitable amphiphilic micelles containing a hydrophobic core and hydrophilic shell, which demonstrated high loading capacity for CPT while maintaining HCV antiviral activity and reducing cytotoxicity [20].

Cationic liposomes, particularly cholesterol-based types, are well suited for clinical application due to the decreased toxicity. Vitamin E (α-tocopherol) is rich with lipid-soluble antioxidants, with physiological pathways that can facilitate targeted delivery from the serum to the liver. Vitamin E was attached to cholesterol-based cationic liposomes and used to effectively deliver inhibitory siRNA specifically to the liver in mouse models. Both HCV core antigen production and firefly luciferase activity were suppressed [21].

Influenza

Influenza is a highly infectious respiratory disease with epidemics which are associated with morbidity worldwide, while annual epidemics and sporadic pandemics results in the deaths of millions of people. Antigenic shifts and mutations of the genome between different species of influenza were resultsin the high degree of variation. thereby enabling the emergence of novel influenza strains and drug resistance. The emergence of new strains continues to pose a public health threat [22].

STP702 (FluquitTM) from Sirnaomics is a polymer-based nanotherapeutic which is currently under preclinical investigation. This incorporates siRNA targeting the conserved regions of influenza for effective antiviral activity against H5N1 (avian flu), H1N1 (swine flu), and newly emerging H7N9. ‘Nanotrap’ particles are thermoresponsive hydrogels which are capable of capturing live infectious virus, viral RNA, and viral proteins. This type of novel technology can be extended to treatment of infectious diseases such as the influenza virus [23].

Hemagglutinin (HA) and neuraminidase (NA) are influenza glycoproteins, which function in viral attachment (to sialic-acid containing receptors on the cell surface) and release, respectively. Oseltamivir is a NA inhibitor that inhibits cell–cell spread and ongoing influenza transmission from occurring.In a study by Li *et al*., [24]. oseltamivir-modified silver nanoparticles were shown to efficiently decrease H1N1 infection by inhibiting both HA and NA activities, *in vitro*. It was shown that prevention of DNA fragmentation, chromatin condensation, and caspase-3 activity also contributed to the antiviral properties of these nano-constructs. The toxicity profiles of these oseltamivir-modified silver nanoparticles, evaluated by cytopathic effect, transmission electron microscopy, and cell viability assays, were also demonstrated to be enhanced in MDCK cells, when compared to oseltamivir controls [24].

In another study, titanium dioxide (TiO2) nanoparticles functionalized with DNA fragments targeting the 3′ non-coding region of influenza a virus were synthesized using a polylysine linker. These nanocomposites were able to enter cells without transfection agents and were demonstrated to be efficient inhibitors of influenza a virus, *in vitro*. Control samples containing random DNA sequences, unbound DNA fragments in the presence of nanoparticles, and naked nanoparticles showed minor antiviral effects [25].

HSV

HSV is the causative agent of orofacial lesions, encephalitis (HSV-1), genital (HSV-2) infections, or disseminated disease. The standard treatment for HSV infections is acyclovir, with valacyclovir and famciclovir being precursor drugs with better bioavailability. Acyclovir is used for the management of HSV with treatment modalities including oral, parenteral, or topical application. There are, however, limitations associated with these treatment modes, which include poor oral bioavailability (15–30%), poor patient compliance, and low skin permeability, respectively. Buccal administration of drugs provides an alternative route to improve efficiency and absorption of otherwise poorly absorbed drugs [26]. Nanospheres were evaluated as delivery agents for the buccal delivery of acyclovir in an effort to increase bioavailability. *In vivo* studies in rabbits showed a marked increase in the absorption of acyclovir-loaded nanospheres with peak plasma concentrations three fold higher than the free drug using oral dosing. The results also showed that the maximum drug concentration was prolonged (6 h versus 2 h), and this can reduce the frequency of drug administration [27].

Several studies have demonstrated increased HSV inhibition using acyclovir-loaded nanoparticles, and the inherent antiviral action of silver nanoparticles. Increased bioavailability was also demonstrated in nanoparticles loaded with anti-herpetic siRNA in mice and acyclovir in rabbits.28Another recent study conducted in rat models, showed that hybrid polymeric nanoparticles loaded with acyclovir effectively improved permeability through vaginal membranes, and can increase the tissue distribution and bioavailability compared to the free drug. This will have important implications for the clinical therapy of HSV in the female population [29].

Human papillomavirus

Epithelial cells are the target cells for human papillomavirus (HPV) infection and can result in a range of symptoms, varying from common warts to cervical neoplasia and cancer. There are more than 100 types of HPV that have been classified, with only a subset being identified as high-risk [30].

STP909 (Cervisil ®) is a nanobased drug candidate, which incorporates siRNA for the treatment of HPV16 and HPV 18 - two of the high-risk genotypes accounting for approximately 70% of cervical cancer cases. The results of *in vitro* studies show that strong duplexes are formed with the mRNA from the E7 genes in both HPV16 and HPV18, while *in vivo* rabbit studies demonstrate that these nanoparticles exert their antiviral activity by knock-down technology of the E7 gene [31].

Nano Vaccines

Nano Vaccinology has applications in both prophylactic and therapeutic approaches and can be used to either increase antigen processing or presentation and/or as an immunostimulatory adjuvant. This approach offers many advantages over traditional vaccine design; it has the potential to overcome the limitations associated with conventional vaccines (weak immunogenicity, intrinsic *in vivo* instability, toxicity and the requirement of multiple administrations).

The enhanced humoral and cellular immune response that is elicited by nano based vaccines is due to the smaller size – which increases uptake by phagocytic cells, the gut-associated lymphoid tissue, and the mucosa-associated lymphoid tissue. This subsequently leads to enhanced antigen recognition and presentation.

Surface modification of these nanocarriers with targeting moieties (peptides, carbohydrates, or antibodies) can facilitate specific and selective immune responses by targeting specific receptors on the surface of various immune cells. An additional benefit of incorporating nanoparticles in vaccine formulations is accomplishing slow and sustained release of antigens or adjuvants [32].

Nanoparticle uptake

Nanoparticle size is a major determinant of cellular uptake with approximately 50 nm in diameter being optimum for non-phagocytic cells. Various ligands (proteins or peptides) can be used to enhance cellular uptake can be used to facilitate cellular entry. They increase the surface charge of nanoparticle can result in increased uptake across cellular membranes.

The size of the nanoparticle also determines the mechanism by which nanoparticles enter the cells and where it subsequently localizes intracellularly. It has recently been demonstrated that the shape of nanoparticles is also a determining factor of the mechanism of uptake. Therefore, knowledge of both of these aspects is invaluable in the engineering of nanoparticles targeted to specific micro-environments [33].

Nanoparticle biodegradation and elimination

Several factors, such as polymer composition, tacticity, hydrophobicity/hydrophilicity profiles, particle size, and molecular weight, can affect the rate of degradation. Eventually, nanoparticles must exit the cell (via exocytosis) if biodegradation did not occur. The rate of exocytosis depends largely on nanoparticle composition and surface properties. For instance, cationic particles that tend to agglomerate intracellularly have a slower rate of elimination compared to PEGylated particles that avoid protein interaction and subsequent agglomeration [34].

Some nanoparticles may be too large to undergo renal clearance and can accumulate in the body since they cannot be degraded [3]. Uptake by macrophages of the mononuclear phagocytic system (MPS) can then modify/increase blood circulation time. This also has important implications for viruses such as HIV, which infect and reside in this cells [35].

Limitations of nanoparticles as therapeutics

1. They were having poor permeability of biological membranes.
2. They were having limiting uptake and utility.
3. Certain physical processes that enable contact between nanoparticle surfaces can cause aggregation of nanoparticles, thereby resulting in clusters, which renders the particles larger than the nanometer range. This has important implications for the uptake, persistence, toxicity, fate, and mobility of nanoparticles.
4. Toxicity concerns include the effects of nanoparticle accumulation, circulation time, and subsequent slow elimination or clearance. Nanoparticle toxicity can potentially result in pulmonary toxicity, renal and hepatotoxicity, neurotoxicity, and spermatoxicity [36].

Conclusion and future perspective

The recent advances in nanomedicine [ability to encapsulate or incorporate drugs with surface modification, targeted drug delivery, biocompatibility, and the ability to achieve slow and sustained drug release] offer superior therapeutic potential, compared to conventional approaches. These modifications can overcome common limitations associated with nanoparticles for biomedical applications, including increased permeability of biological membranes with associated specific uptake, and decreased toxicity profiles. Similarly, poorly water soluble and unstable drugs can be modified and complexed with nanocarriers to achieve improved solubility and stability under physiological conditions.

Future research should explore the possibility of (1) multi-functionalization to achieve concurrent drug delivery and imaging (via a fluorescent signal, for example), to determine *in vitro* localization, and specific cell/tissue/compartment targeting (using targeting ligands like peptides and proteins or molecular recognition strategies, for example) and (2) multiplexing, in order to increase the spectrum of disease that can be treated in heterogeneous populations, by simple, reliable and cost-effective methods. Improvements of currently available conventional antivirals should also be explored using advances in nanotechnology. As previously discussed, 'nanotraps' having illustrated effective inhibition of influenza viruses. This can be extended to other viruses such as HIV, hepatitis, and so on by specifically modifying the attachment carbohydrates of the defined host receptors. To this end, further research and development of these particles are required.

The incorporation of nanotechnology for the treatment of infectious disease offers enormous potential for enhanced mechanisms of action of currently available therapeutics, or the development of novel therapeutics, both of which are desperately required in an era of drug resistance. Despite the various advantages that these nanoparticles have compared to conventional therapies, investigation into the toxicities and potential deleterious effects of certain nanosystems are still required.

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