Quantum dots against SARS-CoV-2: diagnostic and therapeutic potentials

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Abstract

The application of quantum dots (QDs) for detecting and treating various types of coronaviruses is very promising, as their low toxicity and high surface performance make them superior among other nanomaterials; in conjugation with fluorescent probes they are promising semiconductor nanomaterials for the detection of various cellular processes and viral infections. In view of the successful results for inhibiting SARS-CoV-2, functional QDs could serve eminent role in the growth of safe nanotherapy for the cure of viral infections in the near future; their large surface areas help bind numerous molecules post-synthetically. Functionalized QDs with high functionality, targeted selectivity, stability and less cytotoxicity can be employed for highly sensitive co-delivery and imaging/diagnosis. Besides, due to the importance of safety and toxicity issues, QDs prepared from plant sources (e.g. curcumin) are much more attractive, as they provide good biocompatibility and low toxicity. In this review, the recent developments pertaining to the diagnostic and inhibitory potentials of QDs against SARS-CoV-2 are deliberated including important challenges and future outlooks. © 2022 Society of Chemical Industry (SCI).

Keywords: biochemical engineering; bioprocesses; disinfection; removal

INTRODUCTION

Various therapeutic strategies and interventions are being advanced to identify an effective drug for COVID-19 (coronavirus disease 2019) therapy, this disease being instigated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1-4 Nanotechnology-based strategies can be deployed for designing and developing innovative antivirals delivery systems, nanovaccines and (nano)biosensors.5,6 Indeed, nanomaterials and...
nanoarchitectures with unique physicochemical properties can assist in the development of diagnostic tools with sensitivity/selectivity, simplicity and scalability for expeditious and economical detection of SARS-CoV-2.7-9 On the other hand, smart antivirals delivery systems using various nanomaterials can assist in reducing the side effects and improve targeting/selectivity features.10,11 Nanotechnology-centered assays have been evaluated in clinical studies to battle various viral infections, including respiratory viruses, herpes simplex, Ebola virus disease, human immunodeficiency virus (HIV) and others.12-14 Several antiviral drugs have been explored against SARS-CoV-2, but with low solubility in water and some severe side effects comprising low selectivity and targeting properties, restrict their clinical applications.15-18

Quantum dots (QDs) are a desirable option for interaction with viruses as they preventing their entry into cells because of their ease of functionalization with a variety of functional groups and their high surface-to-volume ratio.19-24 Notably, QDs have been integrated in various nano-based treatment and diagnostic tactics, including (bio)imaging, antiviral drug delivery, medical countermeasures and noninvasive visualization of respiratory viral infections (Fig. 1).25 Functionalized QDs can disturb the virus–host cell recognition by interacting with the spike protein of CoVs.26 Since the corona pandemic, numerous studies have pursued the design of functionalized QDs for diagnosing and treating COVID-19 (Fig. 2), by targeting viruses and inhibiting or nebulizing their activities; various innovative QDs designed for inhibiting pathogenic viruses are presented in Table 1.

A large number of articles have appeared pertaining to the overview of the diagnosis and treatment of SARS-CoV-227-30; however, scant attention has been paid to the antiviral and diagnostic applications of QDs. In this review, recent diagnostic and inhibitory strategies and technologies based on functionalized QDs against SARS-CoV-2 are comprehensively discussed with an

Figure 1. Some important advantages of QDs for designing smart nano-systems against SARS-CoV-2.

Figure 2. QDs with attractive potential for the inhibition and analysis of SARS-CoV-2.
emphasize on important challenges and future perspectives; various smart nanosystems have been constructed based on QDs for drug and vaccine delivery. Also, the improvement of QD-based biosensors and their use in (bio)sensing appliances are reviewed.

**QDs AGAINST SARS-CoV-2: DIAGNOSIS AND INHIBITION**

The unique characteristics of QDs allow their deployment for the sensitive detection and inhibition of SARS-CoV-2, which can assist in restraining pandemic conditions. By conjugating QDs (ca 1–10 nm) with highly fluorescent probes, they became suitable for detecting and lasting fluorescence imaging of various cellular processes.\(^27,36,37\) Notably, carbon QDs (CQDs) with advantages of simple functionalization/modification procedures, low-cost synthesis techniques, lower toxicity, good photoluminescence properties, water solubility and good stability can be considered as promising candidates against pathogenic viruses and antibiotic-resistant bacteria.\(^34,38\) These QDs with significant photoluminescence properties have been deployed for labeling pathogenic viruses to understand important underlying mechanisms for viral infections\(^39\); one of the critical challenges is efficient internal viral components labeling with no envelope/capsid alterations. Alternatively, CQDs have suitable applicability for inhibiting the proliferation of pathogenic viruses.

**Diagnostic applications**

Chiral plasmonic nanoparticles (NPs) assembled with QDs have an important role in nanohybrid structures with optical resonances via far-field coupling and near-field mechanisms and improved chiroptical properties.\(^40\) For instance, a chiro-immunosensor with high sensitivity was constructed deploying QDs and chiral gold (Au) nanohybrids.\(^40\) The creation of asymmetric plasmonic chiral nanostructures was accomplished based on self-assembly methods, extending the spectral span of circular dichroism reaction to attain exclusive plasmonic resonant connection with the energized state of QD to help acquire low values of LOD (limit of detection). The constructed probe was employed for detecting picomolar levels of avian influenza A viral \(\text{H}_9\text{N}_2\) strengths, with high sensitivity. Accordingly, this sensing system was evaluated for its practicability on various virus cultures such as avian influenza A \(\text{H}_9\text{N}_2\), fowl adenovirus and CoVs in samples of blood. It was indicated that exciton–plasmon exchanges could alter the chirality; thus the application of assembled nanostructures can be considered as an appropriate and efficient technique for improving the sensitivity of plasmonic (nano)sensors.\(^40\)

In another study, chiral zirconium (Zr) QDs were assembled using \(\text{L}(+)\)-ascorbic acid (Fig. 3),\(^41\) displaying fluorescence and circular dichroism properties. Additionally, these QDs could be coupled with bronchitis virus (IBV) antibodies of CoVs that are anti-infectious to produce an immuno-link in the presence of the anti-IBV antibody-coupled magneto-plasmonic NPs and marked analyte; prepared nanohybrids showed high sensitivity for CoVs with LOD of about 79.15 EID/50 \(\mu\text{L}\).\(^31\) This bioassay was suggested to attain improved sensitivity for IBV detection by as-prepared Zr QDs in blood media, showing higher sensitivity than the traditional ELISA assay.

Due to the small size of QDs and their amenable surfaces, they certainly can be functionalized with various types of biocompatible molecules as exemplified by the attention focused on the development of QD-based Förster resonance energy transfer (FRET) biosensing systems with different energy transfer partners.\(^42,43\) Gorshkov et al.\(^44\) established a FRET-based biosensor to investigate the interactions of SARS-CoV-2 with angiotensin-converting enzyme 2 (ACE2) of the target cells; the fluorescence of the QDs was quenched upon binding with ACE2-conjugated Au NPs. The recovery of fluorescence occurred when the binding of the QDs-receptor-binding domain (RBD) spike protein to ACE2–Au NPs was blocked. The imaging process illustrated the possible capability of internalization of QDs–RBD through clathrin-dependent receptor-mediated endocytosis, with great attraction to ACE2. This nano平台 can be considered as a fast and highly sensitive biosensor in the diagnosis of CoVs.\(^44\)

For the recognition of SARS-CoV-2 RNA, a CdTe QDs–DNA nanobiosensor was constructed via a ligand-exchange technique (Fig. 4).\(^45\) Consequently, the complementary DNA sequence (DNA targeted) was arranged founded on a considerable part of the SARS-CoV-2 genome; the oligonucleotides of the QDs–DNA nanoprobes were constructed to supplement it. This nanosensor could be deployed for the rapid recognition of RNA from SARS-CoV-2 in real samples with outcomes comparable to those of the reverse transcription polymerase chain reaction technique; high specificity and sensitivity (LOD was \(ca 2.52 \times 10^{-9} \text{ mol L}^{-1}\) could be observed.\(^45\) The presence of thiolate captured DNA oligonucleotides on the surface of QDs managed to improve the negative charge of dots, thus increasing the interactions of the captured DNA with QDs. This nanosensor was effectively employed to identify the RNA from SARS-CoV-2 virus, providing promising potentials for clinical diagnostic systems.

The electrochemical aptasensors are sensing devices where an aptamer probe is applied as the recognizer component which is placed on the surface of an electrode; binding of aptamer to the target transpires with great affinity. With the attainment of this binding on the surface of the electrode, the electrode then
exchanges electrons between them. Since aptamers are small in size compared to antibodies, a larger number of them can be immobilized on the surface of the transducer. In one study, an innovative photoelectrochemical aptasensor was developed for sensitive detection of SARS-CoV-2 RBD within 0.5–32.0 nmol L\(^{-1}\) with LOD of ca 0.12 nmol L\(^{-1}\). CdS QDs and graphitic carbon nitride (g-C\(_3\)N\(_4\)) were admixed with a solution comprising chitosan polymer to form chitosan/CdS–g-C\(_3\)N\(_4\) nanocomposites. Next, an indium tin oxide electrode surface was altered with the prepared nanocomposites; the immobilization of amine-bearing aptamer probes was performed on the electrode surface by applying an amine–amine crosslinker.

**Figure 3.** Production of nanohybrid sensor using chiral Zr QDs and IBV antibodies of CoVs. PL: photoluminescence. Reproduced with permission from Ahmed et al.\(^{41}\)

**Figure 4.** Fluorescence CdTe QDs–DNA nanobiosensor for the uncovering of complementary target DNA originated from SARS-CoV-2. Quencher DNA (BHQ\(_2\)-labeled DNA). Reproduced with permission from Bardajee et al.\(^{45}\) Copyright 2021 American Chemical Society.
glutaraldehyde (Fig. 5). Additionally, an innovative and devoid of label surface plasmon resonance (SPR) aptasensor was designed for detecting N-gene of SARS-CoV-2 by applying thiol-altered niobium carbide (Nb2C) MXene QDs as bioplatform for attaching N-gene-targeted aptamer; the immobilized aptamer parts altered their conformation for exclusive binding with N-gene, in the presence of SARS-CoV-2 N-gene. The prepared aptasensor demonstrated LOD of 4.9 pg mL\(^{-1}\) for N-gene in the concentration span from 0.05 to 100 ng mL\(^{-1}\). This sensor exhibited outstanding discernment in the presence of various respiratory viruses in serum. Furthermore, this SPR aptasensor exhibited a practical use in the qualitative analysis of N-gene from assorted samples.

QDs are outstanding fluorescent materials with unique optical and electrical properties. Thus, by doping of a larger amount of QDs, the fluorescence intensity and stability of QD nanobeads (QBs) are expressively greater compared to QDs, which can efficiently increase the sensitivity of a recognition assay. Recently, point-of-care test (POCT) technologies were developed for rapid detection of pandemic viral infections. In one study, a transportable smartphone-based quantum barcode serological assay appliance was designed for the real-time monitoring of patients with SARS-CoV-2 at various sampling times and infectious severities (Fig. 6). The obtained clinical sensitivity was about 90% and the related specificity was 100% for the virus, in comparison with the results obtained from lateral flow assays (sensitivity of 34% and specificity of 100%). This introduced appliance and assay allow real-time evaluation of SARS-CoV-2 infection (analysis of immunity).

Lateral flow immunoassay (LFA)-based POCT systems are amongst quickly growing approaches for qualitative analysis. Although the development of colloidal Au NPs–LFA has many applications in the POCT method, it has low sensitivity as it is based on colorimetry assay. Due to outstanding optical

Figure 5. Mechanism for separating photogenerated electron–hole pairs among g-C3N4 and CdS QDs of a designed aptasensor, (a) before and (b) after SARS-CoV-2 RBD incubation with aptamer probes. Reproduced with permission from Tabrizi et al.
properties, including computable fluorescence intensity, QDs are widely used in LFIA systems as fluorescence tags to improve sensitivity. For instance, Wang et al. designed a colorimetric–fluorescent dual-LFIA biosensor using QBs where the developed SiO$_2$@Au@QBs were conjugated with spike protein. In this strip, a small sample volume of about 1 μL was utilized and the strips contained two test lines (IgM and human IgG) and a rapid detection control line (Fig. 7). This method demonstrated much higher sensitivity (ca 100 times) than those based on Au NPs.

Additionally, the measurements of anti-virus IgM/IgG can be performed quantitatively using QD fluorescence with colorimetric assay.

The application of Fe$_3$O$_4$ nanospheres and QBs can be useful to create a fluorescence-linked immunosorbent assay (FLISA) to identify IgG and such a FLISA assay via QDs has been used to identify anti-COVID-19 IgG. A sandwich detecting technique was deployed based on rabbit antihuman IgG-attached QDs, mouse and antihuman IgG-conjugated Fe$_3$O$_4$ nanospheres. In
the presence of the anti-CoV IgG, the sandwich complex was created and the fluorescence intensity could be investigated after magnetic separation; FLISA afforded a detection limit of 4 pg mL$^{-1}$, which differs from ELISA results, as this method is more sensitive among others, including LFIA and colorimetric assays.\textsuperscript{58} In another study, polystyrene nanobeads were employed for the synthesis of QD-based fluorescent nanobeads. One of the advantages of this method is that the loading of QDs on polystyrene nanobeads avoided the time consumed in formulating silica-based QBs; sensitivity of lower than 25 PFU mL$^{-1}$ was achieved for the recognition of H3N1 virus. Additionally, LFIA assay for SARS-CoV-2 antibody exposure has been developed using the synthesized QD-based fluorescent nanobeads, with improved diagnostic sensitivity (Fig. 8).\textsuperscript{59}

The developed immunochromatographic assay (ICA) is a POCT technology with the advantages of cost-effectiveness, rapidity and uncomplicated process that has been broadly applied in clinical trials. Indeed, the development of an ICA-based assay for respiratory virus is an ideal to increase the detection ability of SARS-CoV-2/FluA infections.\textsuperscript{60,61} A two-channel fluorescent ICA was introduced for the expeditious recognition of SARS-CoV-2 with high selectivity/sensitivity, good stability, significant fluorescence signals and suitable surface functionalization. Consequenly, nanobeads of QDs were produced by adsorption of dense QD multilayers onto the surfaces of SiO$_2$ (ca 180 nm). The determination of SARS-CoV-2 was obtained in 15 min with LOD of 5 pg mL$^{-1}$ (Fig. 9).\textsuperscript{62}

A SARS-CoV-2 antibody-linked magnetic graphene QD-built magnetic relaxation switch was created for the specific recognition of SARS-CoV-2 (Fig. 10(a)).\textsuperscript{63} The probe of the magnetic relaxation switch could be directly admixed with a test sample in a vial that is completely sealed. The operation that is devoid of sample pretreatment mainly diminished the risk to testers for infection throughout the process. The one-step closed-tube technique to identify SARS-CoV-2 was designed with ultralow-field homemade NMR relaxometry functioning at 118 $\mu$T. As a result, the magnetic graphene QD-centered probe demonstrated significant sensitivity for detecting SARS-CoV-2 because of the elevated magnetic relaxivity; the LOD was optimized to 248 particles per milliliter. Notably, the recognition period in the ultralow-field NMR system was barely 2 min, increasing the detection efficiency.\textsuperscript{63} Remarkably simple and rapid detection techniques with high sensitivity and accuracy have been developed for screening total antibody concentrations. In one study, highly luminescent QBs were constructed by embedding QDs into a polymer matrix (Fig. 10(b)).\textsuperscript{64} The prepared nanosystem was deployed as a signal-augmentation marker in LFIA. These QBs were applied for the determination of complete antibody levels in sera by good
features of a double-antigen sandwich immunoassay, and subsequent covalent connection with the conveyed recombinant SARS-CoV-2 spike protein. Consequently, the introduced technique could detect SARS-CoV-2 total antibodies rapidly (ca 15 min) with enhancement in analytical sensitivity of approximately one order of magnitude relative to the applied Au NP-based LFIA. After clinical evaluations, it was revealed that the designed QB-based immunoassay had promising results, especially in dynamic screening of SARS-CoV-2 antibody level in serum (in the whole period of infection).64

In general, QDs display exclusive photochemical and photophysical properties, and thus have pronounced benefits as fluorescence probes in optical biosensing over a wide range of biosensing applications. The functionalization and conjugation approaches will help in maintaining the specificity of QD-based in vitro and in vivo biosensing methods. They have unique chemical and optical properties, such as prolonged fluorescence lifespan, regulated particle sizes, emission of multiple fluorescence wavelengths and wide excitation spectra. QDs and carbon dots (CDs) with effective photoluminescence properties have been used to label pathogenic viruses to investigate the significant mechanisms in viral infections, such as COVID-19 infection. The combination of QDs with various metallic NPs like Au NPs, magnetic NPs, SiO₂, CsS, etc., has been applied to improve the sensitivity of pathogenic virus detection.

Fluorescence-based techniques involving QDs such as FRET for highly effective detection of COVID-19 display detection resolutions far outside the limitations of optical resolution. Nevertheless, QD-based FRET biosensors have not been highly successful in a commercial situation in view of the low sensitivity and efficiency compared with commercial dyes. The combination of QDs with optical and electrochemical aptasensors can be applied to attain great sensitivity and low LOD for the detection of viruses. SPR-based aptasensors are deployable as a method with greatly enhanced sensitivity for the label-free detection of biomolecules. Aptamer-based SPR and electrochemical biosensors have attracted major consideration, due to their cost-effectiveness, greenness and simplicity of procedures. However, aptasensors for the detection of virus such as SARS-CoV-2 have various challenges: for example, the effect of many factors that influence aptamer selection efficacy.

The application of QDs, in combination with other optical and electrochemical properties, would help to increase the sensitivity of bioanalysis systems for their deployment in POCT such as LFIA as a fluorescence tag for accurate and personal diagnosis. QBs can be created via the encapsulation of QDs into a silica and polymer, offering great luminescence properties. They can be employed in the ICA as a POCT technology with the advantages of cost-effectiveness, rapidity and simple process, and could be extensively used in the detection of SARS-CoV-2 infections directly from specimens without sample pretreatment stages, thus offering rapid results. Despite the advantages of QDs in biosensors, they are encumbered with various restrictions in biological applications, such as water solubility and their surface properties. The photoluminescence mechanism of CDs still remains vague, which restricts the design of CDs with fluorescence properties. CDs with long excitation wavelengths are still absent, which inhibits the usages of CDs in vivo due to the low tissue penetration ability of CDs at
short excitation/emission wavelengths. Thus, fabricating CDs with optimal fluorescence and optical properties is imperative.

**Inhibitory applications**

The development of drugs and vaccines against COVID-19 requires comprehensive study and systematic analysis of the functional mechanisms related to the virus. Consequently, it is crucial to detect virus proteins and surface antigens, including SARS-CoV nucleocapsid (N), spike (S) glycoprotein and envelope (E). QD-based probes can enable CoV viral identification and confirmation of inhibitors of the ACE2 receptor binding and SARS-CoV-2 S protein. Generally, the viral infection cycle instigates changes in the structure of the host cell, which in turn causes cell damage. Therefore, for obstructing the viral infection and reducing the spread of infection, the easiest pathway is to enhance the interaction of drugs/inhibitor agents with infected cells or viral replication. In one study, cationic CDs prepared from curcumin demonstrated appropriate antiviral activity, as they could inhibit the proliferation of porcine epidemic diarrhea virus, by altering the surface proteins and prohibiting its entrance into cells. Additionally, they could suppress negative-strand RNA generation and viral budding, and inhibited the amassing of reactive oxygen species by the virus. Cationic CDs could suppress the replication of virus by triggering pro-inflammatory cytokines and interferon-stimulating gene formation. In another study, several water-soluble CQDs were studied for their possible antiviral activity against human CoV (HCoV-229E) infections where they could inactivate viruses in a concentration-dependent manner (half maximal effective concentration (EC50) = 52 ± 8 μg mL⁻¹). The interaction of viral receptors and functional groups of QDs caused the inhibition of viral entrance; the replication of HCoV-229E was likewise obstructed. Additionally, CQDs (ca. 2.1 nm) fabricated from carrageenan and pullulan demonstrated higher anti-proliferative influences against cancer cells as well as promising antiviral activity. The viral inhibition resulting from CQDs of pullulan and carrageenan was 44% and 59%, respectively (Fig. 11). These CQDs with unique physicochemical properties and attractive antiviral effects can be considered as suitable candidates against SARS-CoV-2.

CDs have shown biocompatibility and low cytotoxicity as exemplified by their toxicity analysis on HeLa cells after 24 h of incubation, which exhibited more than 90% cell survival. Additionally, according to the functional groups on the surface of QDs comprising carboxylic and hydroxyl groups, they could interact with...
viral structural proteins. Phenylboronic acid–CQDs were evidenced to be operative against HIV infections. Besides, positively charged CQDs with amine groups strongly inhibited viral infectivity. As an example, polyamine-modified CQDs demonstrated robust antibacterial activity versus white spot syndrome virus envelope by preventing viral infection. Indeed, the results indicated that polyamine-based CQDs could upregulate various shrimp immune genes. Benzoxazine-based CQDs could block the replication of adenovirus-associated viruses and parvoviruses as these complexes attached to the virus surface and inhibited virion functionality in the initial stage of virus activity. The cationic surface charge of QDs can intermingle with the genome of SARS-CoV-2, thus affecting the production of reactive oxygen species in the virus, avoiding RNA replication.

Figure 10. (a) SARS-CoV-2 detection process using magnetic graphene QDs with ultralow-field NMR relaxometry. Reproduced with permission from Li et al. (b) QB-based LFIA (i) with the results from the corresponding tests (ii). RSSP: recombinant SARS-CoV-2 spike protein; BSA: bovine serum albumin; DIG-mAb: anti-digoxin-monoclonal antibody. Reproduced with permission from Zhou et al.
Some effective inhibitors of SARS-CoV-2 are triazole derivatives, which initiate viral enzyme blocking. CQDs with various multisite inhibitors can be employed for blocking viral entry and replication. In one study, triazole-functionalized heteroatom co-doped CQDs were developed as antiviral agents against SARS-CoV-2 by applying citric acid, borax and p-phenylenediamine (Fig. 12(a)); these QDs illustrated high antiviral performances, and could prevent CoVs or other RNA viruses from entering targeted cells. Additionally, the function of viral enzymes such as 3CLpro and helicase, which are required for virus replication, might be blocked. Alternatively, CQDs could play significant roles in increasing the expression of inflammatory cytokines (Fig. 12(b)).

CQDs or CDs have remarkable antiviral activity against SARS-CoV-2, with good biocompatibility and low toxicity. CDs can inhibit viral replication through activating interferon, and increasing the expression of inflammatory cytokines. They can be either made from boronic acid derivatives or coated with amine groups. Indeed, the cationic surface charge of QDs can interact with the genome of a virus, affecting the synthesis of reactive oxygen species in the virus and disturbing genome replications. Therefore, these functional NPs can offer a new platform for the nanoscale treatment of SARS-CoV-2 infection. However, there are significant challenges in developing CD-based nanosystems for antiviral drug delivery. At present, the low solubility of CDs reduces the release efficiency of many antiviral drugs. Another challenge is the need to maintain the activity of CDs in connection with corona particles, which increases their stability to prevent virus replications.

**QDs FOR DRUG AND VACCINE DELIVERY FORMULATIONS AGAINST COVID-19**

Since the outbreak of CoV, various drugs and potential inhibitors have been evaluated to improve symptoms and treat COVID-19 patients. For instance, favipiravir has been explored for changing the sequence of viral RNAs when being replicated. Additionally, remdesivir, ivermectin, niclosamide, merimepodib, chloroquine and rintatolimod are some other drugs that have been studied against SARS-CoV-2 infection; however, these medications and potential inhibitors have not yet shown sufficient evidence for treatment and enough efficacy against COVID-19, and various systematic evaluations and clinical assessments are needed to verify their effectiveness. On the other hand, to address the delivery limitations of antiviral drugs, such as low water solubility, enhanced likelihood of biodegradation, bile clearance of liver and kidney and reduced bioavailability, it is necessary to use efficient delivery systems. The application of NPs as drug carriers can increase bioavailability, reduce toxicity and diminish the dose of antiviral drugs. Notably, by designing delivery control systems, side effects of drugs can also be reduced. It is essential to develop drug delivery systems that, in addition to increasing drug uptake, provide a good concentration gradient between target organs, especially the lungs, in viral infections. There are different ways of drug administration, such as oral, intravenous and intranasal routes, and it is imperative to select the appropriate path and type of nanomaterials deployed in the treatment of infection.

Recent advances have been made in the progress of nanomaterial-based drug systems against viral diseases, and some of them have been approved. As an example, the application of lipid-based and polymer-based nanomaterials with biodegradable monomers enables the delivery of therapeutic agents through encapsulation of antiviral drugs. Polymeric NPs of small sizes have shown promising capabilities for capillary penetration and uptake through cells, which can improve the concentration of drugs in the targeted sites. Nanomaterials with surfaces functionalized using poly(ethylene glycol) polymers demonstrated a reduction in the decrease of opsonization and improved the biodistribution of...
antiviral drugs in blood circulation. Researchers have developed polymeric NPs loaded with diphyllin, which has been applied as a blocker of vacuolar ATPase, to battle against COVID-19. Rio Bravo virus encapsulated into poly(D,L-lactic acid) NPs was employed as a suitable formulation for treating CoV infection and chronic hepatitis C virus. As a result, continuous injection of the drug (1 week after intravenous injection in mouse) and accumulation of these carriers in the target tissue could lead to highly efficient treatment. The designed system with high efficacy can be further evaluated for the treatment of respiratory infection such as COVID-19.

Among various nanocarriers deployed for biomedical and pharmaceutical applications, QDs as semiconductor nanocrystals are attractive candidates according to their unique properties and suitable biocompatibility/low toxicity. QDs as effectual fluorescent labels can be utilized for designing innovative drug delivery systems to observe the metabolism of drugs in the body due to their exclusive physicochemical properties and low toxicity. The modification of QD surfaces in targeted drug and vaccine delivery performs a significant function in the obstruction, treatment and management of viral infections. As an example, QD-based highly active antiretroviral therapy, amprenavir drug formulation, could across the blood–brain barrier and expressively inhibit HIV-1 replication in infected peripheral blood mononuclear cells. The nanometric size of QDs enabled distribution in the cytoplasm of cells and blood–brain barrier, while their nontoxic nature and biocompatibility could broaden their prospects in drug delivery and imaging against viral infection, especially COVID-19.

An innovative microneedle platform using fluorescent QDs has been constructed for delivering vaccines at the same time in the skin; the microneedle array could effectively deliver a polio vaccine in amounts produced by therapeutic antibody levels. McHugh et al. designed an inexpensive microneedle array, which adapted a smartphone to make a near-infrared imaging system, for delivering vaccines via QD-containing poly(methyl methacrylate) microspheres embedded in dissolvable microneedles in rats. Imaging by a smartphone customized to identify near-infrared light demonstrated that these microneedle-delivered QD patterns stayed bright and could be recognized by a machine learning algorithm even several months after application. Additionally, co-delivery with inactivated poliovirus vaccine created highly neutralizing antibody titers. The results established that nanomaterials comprising ZnS:Al shells and CuInSe2 cores had lower toxicity than PbS QDs. Besides, the QDs illustrated their

![Figure 12. (a) Fabrication of CQDs via hydrothermal method. (b) Mechanism of triazole-functionalized heteroatom (TFH)–CQDs performance against SARS-CoV-2. Reproduced with permission from Garg et al.](wileyonlinelibrary.com/jctb)
CONCLUSIONS AND FUTURE PERSPECTIVES

The outbreak of the COVID-19 pandemic had a damaging effect on entire facets of human life, infecting and killing many people around the globe. Prompt diagnostic strategies as well as timely treatment of CoV infection can have a great influence on reducing the morbidity and death. QDs can be employed in the production of innovative diagnostic devices and nanosystem platforms with good potential compared to conventional ones. These nanomaterials deployed for LFIA systems and colorimetric assays have led to many advances in rapid CoV detection. Additionally, their surface-to-volume ratio is high, which makes them appropriate for designing smart nanosystems. However, for commercial and clinical applications of QDs, there is a need for further investigations; especially, their safety aspects have not been delineated sufficiently to comprehend their interaction with other molecules, for instance nucleic acids. Other challenges pertain to the reproducibility of production, the precise size of NPs for photoluminescence applications as well as waste management and the large number of ensuing byproducts. QDs encapsulated with polymers have shown very little toxicity in cells and in vivo studies.

QDs conjugated with fluorescent probes are promising semiconductor nanomaterials for the detection of various cellular processes and viral contagions. They can be deployed as labels in the study of cellular processes as well as in the production of sensors based on FRET. Besides, the combination of QDs with various metallic nanomaterials has been studied for the detection of pathogenic viruses; they are promising options to interact with viruses and stopping them from entering cells because of the possibility of activating them with a variety of functional groups and their inherent high surface-to-volume ratio. Notably, QDs with good biocompatibility, low cytotoxicity, photostability, simple synthesis and multifunctionality have bright prospects in the design future NP-based antiviral formulations; a brilliant opportunity is still expected for CDs in antiviral therapy, especially in COVID-19 emergencies. However, to accelerate the clinical use of QDs in diagnosis and treatment of COVID-19 many challenges still need to be addressed:

1. More in-depth studies should be performed to investigate metabolic paths, long-term toxicity, biocompatibility and biodegradation. Eco-friendly synthesis methods with natural antiviral agents based on QDs will be an encouraging strategy. Using greener methods to synthesize nontoxic QDs, and deploying natural sources such as plant extracts or microorganisms, can overcome their toxicity and decrease the energy consumption of the involved processes. Besides, surface functionalization can also be considered in order to increase their efficiency.

2. Large-scale production of nanomaterials with high sensitivity, reproducibility and long-term storage stability is still an important challenge; consequently, to overcome these hurdles, it is essential to simplify the synthesis procedures.

3. There are limited studies on the use of QDs to diagnose SARS-CoV-2 with the assistance of a microfluidic-based system by conjugation of QDs on the surface of active molecules. Therefore, systematic explorations and commercialization in this field of science are anticipated in the future. Furthermore, affinity-based biosensors could be envisioned for the detection of various viruses in view of the suppleness of QD design and manufacture of microfluidics systems. The combination of biosensors with complementary metal oxide semiconductor and smartphone devices to detect COVID-19 can be deployed for biosensor-based diagnostics.

4. Further efforts are needed for targeted and smart delivery of QDs loaded with drugs and vaccines to cells and tissues in vivo and to find animal models to test the antiviral effect of these NPs. Undoubtedly, the engineered QDs would be able to stabilize therapeutic compounds, improve their plasma circulation time and decrease the concentration of free drugs to diminish their side effects. Additionally, the targeting agents can be covalently bound to the QD surface through cleavable chemical bonds; thus the conjugates could initially evade renal filtration, and then, after the ligands are cleaved, would be small enough to be cleared out of the body. With the continuing developments being planned to recognize novel targeting ligands and the advancements of particular nanomaterials, QD-based nanotechnology will be continuously expanding its list of uses.

5. It is imperative to recognize the extent of mutation of target viruses and to continually update their structural chemistry.

6. Although the low concentrations of NPs are likely to be safe to cells and tissues, it is still necessary to examine the concentration limits of NPs in tissues, particularly in clinical trials. Typically, the toxicity issues and antiviral activities of NPs are dose-dependent. Thus, optimization processes should be performed to obtain the optimal concentration/conditions of each antiviral agent.

CONFLICT OF INTEREST

The authors declare no conflict of interest.
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Non-functional text