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Review article

Novel polymer-based hydrogels of recent research in drug delivery for disease treatment related to SARS-CoV-2 virus

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Abstract. Polymer-based hydrogels are hydrophilic polymer networks with a remarkable capacity to absorb substantial amounts of water and biological fluids, rendering them highly attractive for drug delivery applications. The COVID-19 pandemic has acted as a catalyst for research and innovation in the realm of polymer-based hydrogels for drug delivery, with a particular emphasis on antiviral therapeutics, vaccines, diagnostics, and precision delivery to the respiratory system. The distinctive attributes of hydrogels, such as their biocompatibility, customizable drug release profiles, and ease of functionalization, establish them as versatile platforms for the development of advanced drug delivery systems to combat not only COVID-19 but also a spectrum of other infectious diseases. This study is dedicated to scrutinizing and evaluating the characteristics of polymer-based hydrogels employed in drug delivery for the treatment of diseases associated with the SARS-CoV-2 virus. Furthermore, the investigation introduces a novel classification system for polymer-based hydrogels deployed in drug delivery for SARS-CoV-2-related diseases. Additionally, the paper provides an up-to-date evaluation of the latest developed hydrogels utilized in drug delivery for the treatment of diseases linked to the SARS-CoV-2 virus, based on research conducted through the recent months of 2023.

Keywords: *polymer-based hydrogel, targeted drug delivery, COVID-19, SARS-CoV-2, vaccines*

1. Introduction

The COVID-19 pandemic has presented an array of challenges and given rise to a spectrum of diseases and health issues [1]. Foremost among the challenges of the pandemic is the swift transmission of the SARS-CoV-2 virus [2]. Strategies to curb transmission encompass extensive vaccination campaigns [3], the implementation of public health measures like mask-wearing [4] and social distancing [4], and the promotion of hygiene practices such as frequent handwashing [5]. The SARS-CoV-2 virus, which causes COVID-19, primarily targets the respiratory system [6]. However, it can also precipitate various complications and impact other organs and bodily systems [7]. COVID-19, an abbreviation for Coronavirus Disease 2019, is the ailment brought about by the SARS-CoV-2 virus [8]. It manifests as a broad spectrum of symptoms, spanning from mild to severe respiratory ailments [9]. Common symptoms include fever, cough, shortness of breath, fatigue, loss of taste or smell, and body aches [10]. In severe instances, it can progress to pneumonia and acute

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respiratory distress syndrome (ARDS) [11], a potentially life-threatening condition [12]. Advanced stages of COVID-19 may culminate in ARDS [11], characterized by severe lung inflammation [13], culminating in respiratory failure [14]. ARDS can precipitate breathing difficulties [14], diminished oxygen levels [15], and potentially necessitate mechanical ventilation in intensive care units (ICUs) [16]. Additionally, COVID-19 can incite viral pneumonia [17], an infection that inflames the air sacs in the lungs [17]. Pneumonia can trigger symptoms such as cough [10], difficulty breathing [14], chest pain [17], and fever [13]. COVID-19 has also been linked to an elevated risk of blood clots [18] and abnormal blood clotting [19], leading to conditions like deep vein thrombosis (DVT) [20], pulmonary embolism (PE) [21], and disseminated intravascular coagulation (DIC) [22]. Some individuals infected with SARS-CoV-2 may develop myocarditis [23], an inflammatory condition affecting the heart muscle [24]. Furthermore, COVID-19 can contribute to various cardiac complications [25], including arrhythmias [26], heart failure [25], and acute coronary syndromes [27]. Moreover, COVID-19 can result in acute kidney injury (AKI) in select cases [28], particularly in individuals with severe illness [29]. AKI is characterized by the abrupt loss of kidney function, leading to reduced urine production and the accumulation of waste products in the body [28]. SARS-CoV-2 can also influence the nervous system [30], eliciting a diverse range of neurological symptoms [30]. These encompass loss of taste and smell (anosmia and ageusia) [31], headache [32], dizziness [33], confusion [34], stroke [35], and encephalitis [36]. Some individuals experience persistent symptoms [37] and complications even after recovering from acute COVID-19 infection [38]. This condition, recognized as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC) [39], may entail sustained fatigue [40], respiratory issues [41], cognitive difficulties ('brain fog') [42], and other protracted health problems [38, 40]. It is imperative to note that while these conditions have been linked to COVID-19, not all individuals infected with the virus will encounter these complications. The severity and outcomes can significantly vary among individuals. Timely medical care, vigilant monitoring, and appropriate treatment are pivotal in managing these diseases associated with the SARS-CoV-2 virus.

Drug delivery systems play a pivotal role in treating diseases associated with the SARS-CoV-2 virus. A range of antiviral drugs [8], including remdesivir [43], have been rigorously investigated for their effectiveness against SARS-CoV-2 [8, 43]. These drugs can be administered via diverse routes, including intravenous infusion [44] or oral ingestion [45], contingent on the severity of the disease. Monoclonal antibodies have demonstrated significant promise in neutralizing the SARS-CoV-2 virus and mitigating the severity of COVID-19 [46]. Delivery of these antibodies can be accomplished through intravenous infusion or subcutaneous injection [45]. Vaccines stand out as one of the most potent strategies for preventing COVID-19 and reducing disease severity [47]. Varied vaccine types have been developed, encompassing mRNA-based vaccines (such as Pfizer-BioNTech and Moderna) [48] and viral vector-based vaccines (such as Oxford-AstraZeneca and Johnson & Johnson) [49]. They are typically administered via intramuscular injection [48, 49]. Inhalation drug delivery systems have been explored for precisely delivering antiviral drugs and immune-modulating agents directly to the respiratory system [8, 45]. This approach seeks to transport therapeutics directly to the infection site, amplifying their efficacy and diminishing systemic side effects. Nanoparticles serve as carriers for the targeted conveyance of drugs to infected cells or tissues [50]. They provide safeguarding against drug degradation [51], enhancement of drug stability [52], and augmentation of bioavailability [53]. Delivery systems reliant on nanoparticles can be introduced through different routes, including intravenous injection [45], oral administration [54], or inhalation [55]. Localized drug delivery systems, such as injectable hydrogels or implants [45], have been harnessed to transport therapeutics directly to infection or inflammation sites [56]. These systems ensure the sustained release of drugs [57], maintaining their presence at the target location for an extended duration [58]. Drug delivery systems also facilitate the administration of combination therapies [45], wherein multiple drugs with complementary mechanisms of action are dispensed simultaneously or sequentially [59]. This approach can heighten therapeutic efficacy and help surmount issues related to drug resistance [60].

Polymer-based hydrogels have demonstrated significant potential in the realm of drug delivery for the

treatment of diseases linked to the SARS-CoV-2 virus, notably COVID-19. These hydrogels offer a distinctive array of advantages that aptly tackle the specific challenges associated with delivering therapeutics for viral infections [61]. Polymer-based hydrogels can be meticulously tailored to encapsulate [45] and efficiently deliver antiviral drugs [8], such as remdesivir [43] or protease inhibitors [62], directly to the intended target site [58]. The hydrogel matrix serves as a protective shield, guarding the drug against degradation [63], enhancing its stability [64], and facilitating sustained release [57], thus enabling an extended therapeutic effect [56]. Hydrogels also find utility in conveying immune-modulating agents [8, 45], such as cytokines [65] or immune checkpoint inhibitors [62], for the regulation of the immune response in COVID-19 patients [8]. These hydrogels can orchestrate a localized and meticulously controlled release of immune modulators [8, 45, 57], thereby fostering a targeted and finely balanced immune response [36, 58]. Polymer-based hydrogels are poised for deployment in vaccine delivery against SARS-CoV-2 [48, 49], serving as vaccine carriers [48, 49, 66]. They can vary in type and origin, depending on the specific application and requirements, as shown in Table 1. They facilitate the controlled release of antigens [67] and adjuvants [68], culminating in an augmented immune response [36] and the development of longer-lasting immunity [36, 58]. These hydrogels can be administered through various routes [45], encompassing injectable formulations [69] or mucosal delivery systems [70]. Given the primary respiratory system involvement in COVID-19 [6], pulmonary drug delivery assumes paramount importance [21]. Inhalable polymer-based hydrogels can be meticulously designed to deliver therapeutic agents directly to the lungs [17, 71], thus affording localized treatment while mitigating systemic side effects [45, 71]. These hydrogels can be engineered to possess appropriate rheological properties for efficient aerosolization [72] and deposition within the respiratory tract [6]. Furthermore, polymer-based hydrogels are amenable to customization with targeting ligands [73] or functional groups, enabling precise site-specific delivery [45]. By incorporating targeting moieties that specifically recognize infected cells [45] or receptors involved in viral infection [61], hydrogels can amplify drug accumulation at the intended target site [58]. This enhancement markedly augments therapeutic efficacy [74] while concurrently curtailing off-target effects [45]. Hydrogels have also proven their mettle in the realm of diagnostic platforms for SARS-CoV-2 detection [75]. Tailored hydrogels can be meticulously engineered to capture viral antigens [67] or antibodies [41], thereby enabling sensitive and specific detection of the virus in patient samples [45]. These hydrogel-based diagnostic systems furnish valuable

Table 1. Several types and origins of polymer-based hydrogels used for vaccine delivery against SARS-CoV-2.

Types of polymer based hydrogels	Information for origins of polymer-based hydrogels
Synthetic polymer-based hydrogels	These hydrogels are synthesized from various synthetic polymers, such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), or poly(*N*-isopropylacrylamide) (PNIPAAm) [8, 45]. They are designed with specific properties to enhance vaccine delivery, such as controlled release and protection of vaccine antigens [45].
Natural polymer-based hydrogels	Natural polymers like alginate, chitosan, and hyaluronic acid can be used to create hydrogels for vaccine delivery [8]. These polymers are often biocompatible and can be modified to improve their performance in vaccine delivery systems [45].
Protein-based hydrogels	Some hydrogels are formed from proteins, such as gelatin or collagen [57]. These protein-based hydrogels can be used as carriers for vaccine antigens, and their biocompatibility makes them suitable for vaccine delivery applications [72].
Peptide-based hydrogels	Peptide-based hydrogels, including self-assembling peptides, can be engineered to encapsulate and deliver vaccine antigens. They offer precise control over the release kinetics of the vaccine components [66, 67].
Hybrid hydrogels	Hybrid hydrogels are composed of a combination of synthetic and natural polymers or other materials. These hydrogels can be tailored to exhibit specific characteristics required for vaccine delivery, such as stability and adjuvant properties [81, 82].
Lipid-polymer hybrid hydrogels	These hydrogels combine the advantages of both lipids and polymers. They can be used to encapsulate lipid-based vaccine formulations, making them suitable for lipid nanoparticle-based COVID-19 vaccines [8, 83].
Nanoparticle-loaded hydrogels	Hydrogels can also be engineered to contain nanoparticles, such as mesoporous silica nanoparticles or lipid nanoparticles, which can carry vaccine antigens. These composite systems provide enhanced control over antigen release [84, 85]

contributions to early detection and continuous monitoring of COVID-19 [75]. In instances of severe COVID-19, tissue damage and lung injury can ensue [8, 17, 21]. Polymer-based hydrogels, armed with regenerative properties, find utility in promoting wound healing [76, 77] and facilitating tissue repair [78]. These hydrogels can efficiently transport growth factors [45], cytokines [65], or stem cells to the damaged tissue [79], thereby expediting the healing process [80] and restoring tissue functionality [45]. The development and application of polymer-based hydrogels for diseases linked to the SARS-CoV-2 virus continue to be active areas of research. Researchers are actively exploring innovative hydrogel formulations, optimizing drug release profiles, and incorporating advanced functionalities to enhance treatment outcomes and effectively address specific challenges associated with COVID-19. The inherent versatility and tunability of polymer-based hydrogels render them promising candidates for developing efficacious drug delivery systems tailored to combat viral infections.

This paper endeavors to offer an updated overview of the advancements in polymer-based hydrogel research for drug delivery and the treatment of diseases related to the SARS-CoV-2 virus. Polymer-based hydrogels assume a pivotal role in facilitating effective drug delivery within the context of SARS-CoV-2-related diseases. By scrutinizing recent progressions in fabrication methods and accentuating the exceptional attributes of polymer-based hydrogels, this review aims to illuminate the potential applications and advantages of these hydrogels in mitigating the challenges posed by these diseases. Moreover, this study introduces original insights and novel contributions through a new classification system for polymer-based hydrogels used in drug delivery for SARS-CoV-2-related diseases. It provides an updated evaluation of innovative polymer-based hydrogels utilized in the treatment of diseases associated with the SARS-CoV-2 virus in recent months of 2023.

2. Main factors of drug delivery systems for disease treatment related to SARS-CoV-2 virus

2.1. Traditional drug delivery systems and novel drug delivery systems

Both traditional and novel drug delivery systems play pivotal roles in the treatment of diseases related to the SARS-CoV-2 virus. Traditional drug delivery systems encompass established routes like oral administration, sublingual administration, buccal administration, rectal administration, intramuscular administration, subcutaneous administration, intradermal administration, and intravenous administration [45], as illustrated in Figure 1. These well-established approaches have been widely employed in the management of various diseases, including those induced by SARS-CoV-2.

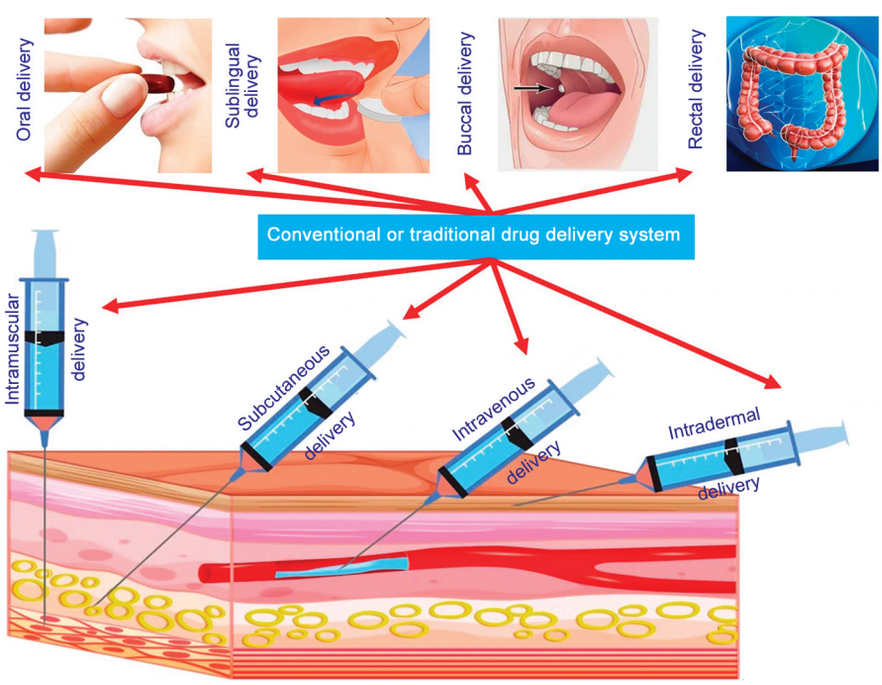

Figure 1. Classification of the conventional or traditional drug delivery systems.

Regarding the SARS-CoV-2 virus, novel drug delivery systems have garnered substantial attention. These pioneering strategies are designed to enhance drug effectiveness, enhance patient compliance, and address specific challenges related to COVID-19 treatment. The novel drug delivery systems encompass innovative methodologies, including rate-preprogrammed delivery, activation-modulated delivery, feedback-regulated delivery, and site-targeting delivery [45], as depicted in Figure 2.

For diseases related to the SARS-CoV-2 virus, the choice between conventional and novel drug delivery systems depends on factors such as the specific therapeutic agent, the desired site of action, and the desired pharmacokinetic profile.

Nature of therapeutic agents: for SARS-CoV-2 virus-related diseases, therapeutic agents can vary widely. These may include antiviral drugs, vaccines, monoclonal antibodies, or small molecules that target specific pathways involved in the infection [8]. The choice of delivery system depends on the type of therapeutic agent, including antiviral drugs, vaccines, and monoclonal antibodies. Some antiviral drugs may require sustained and controlled release to maintain effective drug concentrations in the body [45]. Novel drug delivery systems, such as hydrogels, can provide this controlled release, ensuring a consistent therapeutic effect over time. Vaccines often require precise delivery to the immune system to generate an immune response [8]. Conventional routes like intramuscular or subcutaneous injections are commonly used. However, novel vaccine delivery systems, including hydrogel-based formulations, can offer advantages such as improved stability and mucosal delivery [45]. For monoclonal antibodies, these large molecules often require parenteral administration. Conventional injections are typical, but novel formulations, including hydrogels, can potentially provide sustained release, reducing the frequency of administration [45].

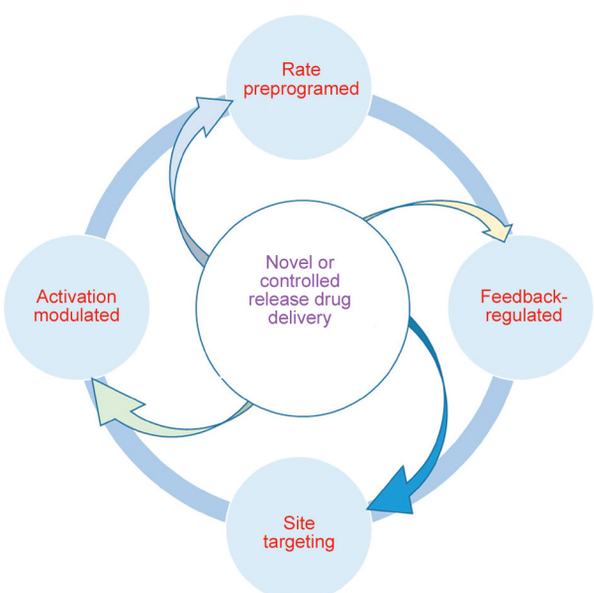

Figure 2. Classification of the novel drug delivery systems.

Desired site of action: depending on the disease stage and target, the desired site of action may vary. For SARS-CoV-2-related diseases, the target sites can include respiratory tissues, mucosal surfaces, or systemic circulation [45]. The choice of delivery system depends on the site of respiratory delivery and systemic delivery. For respiratory delivery, hydrogels can be advantageous for respiratory drug delivery due to their ability to form gels or films that adhere to mucosal surfaces. This is especially relevant for diseases affecting the respiratory tract, like COVID-19 [8]. For systemic delivery, conventional injections are often used for systemic delivery to ensure rapid and reliable drug distribution. However, novel formulations, including hydrogel-based nanoparticles, can provide sustained release for systemic treatments [45].

Pharmacokinetic profile: this required for SARS-CoV-2-related diseases can vary based on the therapeutic agent and disease stage. Some key considerations include sustained release and rapid onset. For certain therapeutic agents, maintaining a consistent drug concentration in the body is crucial for efficacy [45]. Hydrogels can offer sustained release, reducing the need for frequent dosing. In some cases, rapid drug action is essential, especially in acute situations. Conventional drug delivery systems like intravenous injections provide rapid onset. Still, hydrogels can be designed to release drugs quickly when needed [45]. Novel drug delivery systems offer additional advantages, such as targeted delivery [86], sustained release [87], or the ability to overcome biological barriers [45, 88], which can be particularly beneficial in addressing the challenges associated with the treatment of SARS-CoV-2-related diseases. However, conventional drug delivery systems still play an important role, especially for widely used drugs and established routes of administration.

2.2. Stimuli-responsive behaviors and their effects on drug loading and releasing parameters

The drug loading and release characteristics of a drug delivery system are intricately influenced by various environmental conditions, including pH, temperature, ionic strength, solvent properties, drug loading methodologies, and others. These factors collectively play a pivotal role in shaping the performance of drug delivery systems. For instance, alterations in pH and temperature can exert profound effects on drug solubility, potentially enhancing or diminishing it, while variations in ionic strength may modulate electrostatic interactions and drug release kinetics [45, 86, 89]. Consequently, researchers have explored stimuli-responsive drug delivery systems as a strategic approach to precisely control drug release in response to changing environmental cues.

Stimuli-responsive drug delivery systems are ingeniously designed to harness specific triggers, such as alterations in temperature, pH levels, exposure to light, application of magnetic fields, or ultrasound waves, to initiate and modulate drug release [90]. These responsive systems offer a versatile means of achieving controlled drug delivery, thereby optimizing therapeutic outcomes and minimizing side effects [45]. The manner in which drugs are loaded into these systems and subsequently released is intimately intertwined with the chosen stimuli and their respective mechanisms of action.

For instance, consider the case of temperature-responsive polymer-based drug delivery systems, exemplified by poly(*N*-isopropyl acrylamide) [91]. These polymers exhibit a unique behavior wherein they swell at lower temperatures and collapse at higher temperatures. This phase transition property can effectively trap drug molecules within the polymer matrix when exposed to elevated temperatures. In contrast, when the temperature is lowered, the polymer swells again, promoting the release of the entrapped drug. This approach ensures that drug release occurs precisely where and when it is needed. As an example, Figure 3 illustrates the synthesis of polymer-based hydrogels, the encapsulation of drug molecules within the polymer matrix, and the subsequent release of the entrapped drug through temperature-responsive behavior [45, 91].

Light-responsive drug delivery systems incorporate photosensitive compounds, which can respond to specific wavelengths of light. When exposed to light, these substances can trigger changes in the polymer structure or disrupt drug-polymer interactions, resulting in a controlled release of the drug. This offers a highly tunable method for modulating drug release rates and durations [92].

Additionally, magnetic and ultrasound-sensitive drug delivery systems leverage external forces to manipulate drug molecules within the delivery vehicle. Magnetic fields can be employed to direct drug-loaded nanoparticles or carriers to specific target

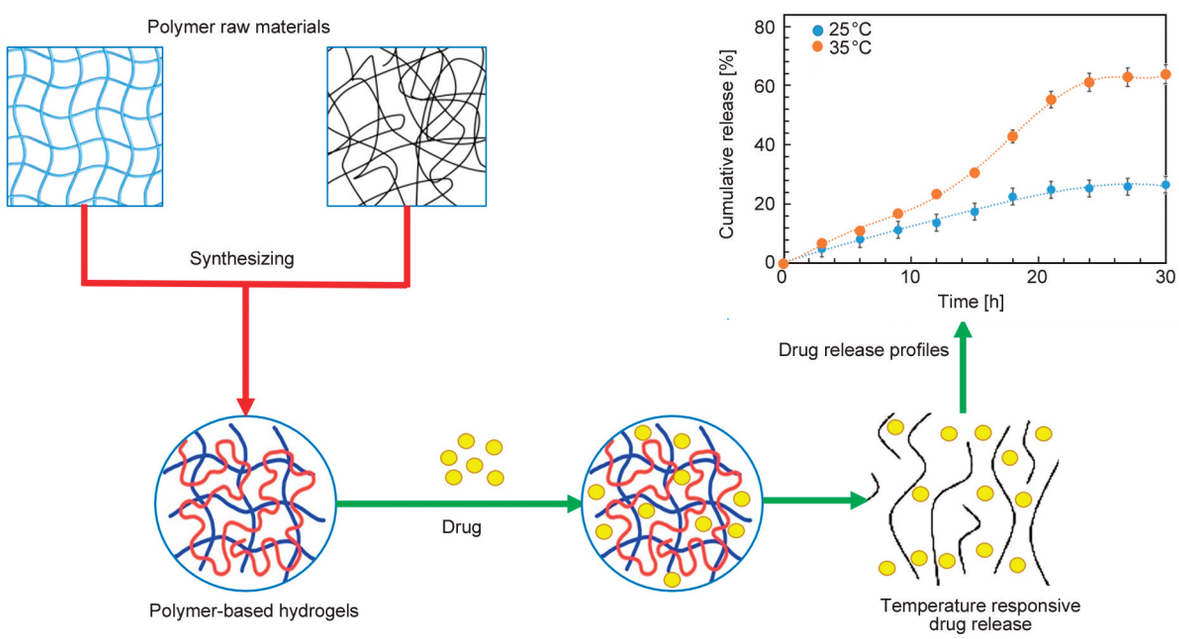

Figure 3. Processes of synthesizing, trapping drug, and releasing drug of temperature-responsive polymer-based hydrogels.

sites within the body, enabling localized and targeted drug delivery [84]. Ultrasound, on the other hand, can facilitate the controlled release of drugs by promoting the disruption of drug carriers or enhancing their permeability at the target site [45]. These modalities provide precise control over drug release, reducing systemic exposure and potential side effects. The design and performance of drug delivery systems are intricately intertwined with the environmental conditions and stimuli-responsive mechanisms they employ. By harnessing these factors, researchers have developed innovative strategies to achieve controlled drug release, offering great promise for enhancing the efficacy and safety of pharmaceutical treatments.

2.3. Carriers in drug delivery systems for disease treatment related to SARS-CoV-2 virus

In the context of disease treatment related to the SARS-CoV-2 virus, various types of carriers are employed in drug delivery systems. These carriers serve as vehicles to transport therapeutic agents to the target site [86], enhance drug stability [52], improve drug solubility [45], and provide controlled release profiles [87]. Some commonly used carriers in drug delivery systems for SARS-CoV-2-related diseases include lipid-based nanoparticles [83], polymeric nanoparticles [93], polymer-based hydrogels [94], viral vectors [49], nanocarriers [83], and anti-body-drug conjugates (ADCs) [95] as illustrated in Figure 4. Polymer-based hydrogels used as carriers in drug delivery systems for the treatment of disease related to SARS-CoV-2 virus are conjugated polymers [94].

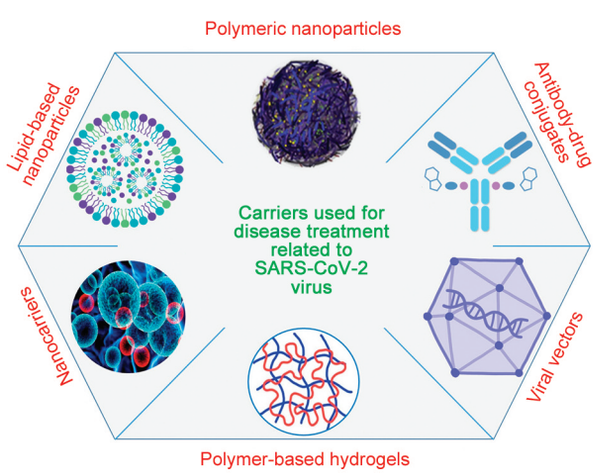

Figure 4. Carriers in drug delivery systems for disease treatment related to the SARS-CoV-2 virus.

They are a class of macromolecules characterized by a π-conjugated sp^2 carbon-based backbone [94]. They are known for their remarkable properties, including intrinsic flexibility, optoelectronic capabilities, and solution processability. These properties make them versatile materials for various applications. Conjugated polymers are classified into two groups: conjugated homopolymers and copolymers. For example, conjugated homopolymers consist of a single species of repeating units, including poly(acetylene); poly(3,4-ethylenedioxythiophene) (PEDOT); poly(thiophene); poly(*p*-phenylenevinylene) (PPV); poly(pyrrole) (PPy); poly(aniline) (PANI) [96]. Another one, conjugated copolymers contain two or more different types of repeating units, which means they are composed of more than one type of monomer such as DPP-DTT; PEDOT:PSS; TBTT-ProDOT [94, 96].

2.3.1. Lipid-based nanoparticles in drug delivery systems for disease treatment related to SARS-CoV-2 virus

Lipid-based nanoparticles are a type of carrier commonly used in drug delivery systems for the treatment of diseases related to the SARS-CoV-2 virus. They are composed of lipid bilayers that encapsulate therapeutic agents, including antiviral drugs [8], nucleic acids [8], or vaccines [8, 83]. They offer several advantages for drug delivery. Lipid-based nanoparticles are biocompatible and well-tolerated by the body, reducing the risk of adverse reactions [97]. The lipid bilayer of these nanoparticles provides protection to the encapsulated drug, shielding it from degradation by enzymes or other harsh conditions in the body [98]. Lipid-based nanoparticles can solubilize hydrophobic drugs, improving their solubility and bioavailability [99]. The lipid bilayers can be engineered to control the release of the encapsulated drug, allowing for sustained and controlled drug delivery over an extended period [100]. The surface of lipid-based nanoparticles can be modified with ligands or antibodies to target specific cells or tissues [99, 100]. This targeting enhances the delivery of drugs to the desired site, increasing therapeutic efficacy and reducing off-target effects. Lipid-based nanoparticles are widely used as carriers for mRNA vaccines against SARS-CoV-2, such as the Pfizer-BioNTech and Moderna COVID-19 vaccines [48]. These nanoparticles encapsulate the mRNA molecules, protecting them from degradation and facilitating their uptake

into cells to produce viral spike proteins and subsequent immune response [101]. The lipid-based nanoparticles offer a versatile platform for drug delivery in the context of SARS-CoV-2-related diseases [100]. They provide a means to enhance drug stability [102], improve solubility [99], control release kinetics [103], and target specific cells or tissues [99, 100], ultimately improving the efficacy and safety of therapeutic interventions.

2.3.2. Polymeric nanoparticles in drug delivery systems for disease treatment related to SARS-CoV-2 virus

Polymeric nanoparticles are another type of carrier widely used in drug delivery systems to treat diseases related to the SARS-CoV-2 virus. These nanoparticles are composed of biocompatible and biodegradable polymers [104, 105], such as poly(lactic-*co*-glycolic acid) (PLGA) [77], polyethylene glycol (PEG) [106], or chitosan [107]. Polymeric nanoparticles can encapsulate a wide range of drugs, including antiviral agents [104], antibodies [108], or nucleic acids [109], protecting them from degradation and improving their stability [77, 106]. The release of the encapsulated drug from polymeric nanoparticles can be finely tuned by modifying the polymer properties, such as molecular weight or composition [104]. This allows for controlled and sustained drug release over an extended period, reducing the frequency of dosing [106]. Polymeric nanoparticles can be functionalized with ligands [104] or antibodies on their surface to specifically target cells or tissues involved in SARS-CoV-2 infection [106–109]. This targeted approach improves drug accumulation at the desired site, enhancing therapeutic efficacy and minimizing off-target effects. The polymeric matrix of nanoparticles provides stability to the encapsulated drug, shielding it from enzymatic degradation and harsh physiological conditions [104]. Some polymeric nanoparticles possess inherent immunomodulatory properties, which can be harnessed to modulate the immune response against SARS-CoV-2 [108]. For example, they can be engineered to elicit specific immune responses or enhance the delivery of vaccines [108]. Polymeric nanoparticles have been extensively explored for vaccine delivery against SARS-CoV-2 [110]. They can encapsulate viral antigens or mRNA molecules, protecting them and facilitating their uptake by immune cells, leading to a potent immune response [104, 110].

Polymeric nanoparticles offer versatility in terms of drug loading, release kinetics, and targeting capabilities, making them valuable tools in the development of drug delivery systems for the treatment of diseases related to the SARS-CoV-2 virus. Their biocompatibility, tunable properties, and potential for immunomodulation make them attractive candidates for delivering therapeutics and vaccines against COVID-19.

2.3.3. Polymer-based hydrogels in drug delivery systems for disease treatment related to SARS-CoV-2 virus

Polymer-based hydrogels are three-dimensional crosslinked polymer networks that can absorb and retain large amounts of water or biological fluids [111]. They have emerged as promising materials in drug delivery systems for the treatment of diseases related to the SARS-CoV-2 virus. The hydrogels can serve as matrices to encapsulate therapeutic agents, including antiviral drugs, antibodies, or nucleic acids [112]. The hydrogel structure provides protection to the encapsulated drugs, preventing degradation [113] and improving their stability [52]. Hydrogels exhibit a unique capability to control the release of drugs over an extended period [45]. They can be engineered to release drugs in a sustained manner, maintaining therapeutic concentrations at the target site and reducing the frequency of dosing [45, 111]. Hydrogels can be designed to achieve targeted drug delivery. By incorporating ligands, antibodies, or specific moieties onto the hydrogel surface, they can selectively interact with target cells or tissues involved in SARS-CoV-2 infection [114]. This enables precise delivery of therapeutics to the desired site, enhancing treatment efficacy and minimizing off-target effects. Hydrogels can be applied topically or implanted at specific sites, allowing for localized drug delivery [45]. In the case of respiratory infections caused by SARS-CoV-2, hydrogels can be formulated as inhalable or intranasal formulations to directly target the respiratory system [114]. Hydrogels can immobilize antiviral agents within their structure, creating a sustained and localized antiviral effect. This approach can help inhibit viral replication and reduce viral load at the infection site [114]. Hydrogels have inherent properties that promote tissue regeneration and wound healing. In the case of SARS-CoV-2-related diseases, hydrogels can aid in repairing damaged lung tissues or supporting the healing of skin lesions caused by infection or medical interventions [115].

Hydrogels offer versatility in terms of their composition, structure, and drug release properties, making them attractive for developing drug delivery systems for the treatment of diseases related to the SARS-CoV-2 virus [114, 115]. Their ability to encapsulate, protect, and release drugs, as well as their potential for targeted and localized therapy, positions them as valuable tools in combating COVID-19 and its associated complications [114, 115].

2.3.4. Viral vectors in drug delivery systems for disease treatment related to SARS-CoV-2 virus

Viral vectors are a type of carrier or delivery system used in gene therapy and vaccine development, including for disease treatment related to the SARS-CoV-2 virus [116]. They are derived from viruses that have been modified to deliver therapeutic genes or antigens into target cells [117]. There are different types of viral vectors commonly used in gene therapy and vaccine development. The two main types are adenoviral vectors [118] and lentiviral vectors [119]. Adenoviral vectors are derived from adenoviruses [118], while lentiviral vectors are derived from lentiviruses, such as the human immunodeficiency virus (HIV) [119, 120]. These vectors have been engineered to be replication-deficient and non-pathogenic, making them safe for therapeutic use [116]. Viral vectors are used to deliver therapeutic genes or genetic material into target cells [117]. In the context of SARS-CoV-2-related diseases, viral vectors can be designed to deliver genes encoding antiviral proteins or immune-stimulatory molecules [117]. These genes can enhance the host's immune response, inhibit viral replication, or modulate cellular pathways involved in the disease. Viral vectors have been employed in the development of vaccines against SARS-CoV-2 [117]. In this approach, the viral vector is engineered to carry a gene encoding a specific antigen from the SARS-CoV-2 virus. When the viral vector is administered, it enters host cells and expresses the antigen, triggering an immune response [116]. This immune response can lead to the production of antibodies and the activation of T-cells, providing protection against the virus [117]. Viral vectors can be designed to target specific cells or tissues. By modifying the viral vector's surface proteins or incorporating targeting ligands, they can selectively bind to receptors on specific cells, enhancing the delivery of therapeutic genes or antigens to the desired target [116, 117]. Although viral vectors have shown promise in drug delivery, safety considerations must be addressed. These include the potential for immune responses against the viral vector itself and the risk of insertional mutagenesis, where the therapeutic gene integrates into the host genome and potentially disrupts normal cellular functions [117]. Extensive preclinical and clinical studies are conducted to evaluate the safety and efficacy of viral vectors in drug delivery systems.

Viral vectors have shown potential as effective carriers in drug delivery systems for the treatment of diseases related to the SARS-CoV-2 virus. They offer the advantage of efficient gene delivery and antigen expression, which can elicit robust immune responses and potentially enhance therapeutic outcomes. However, careful design and evaluation are necessary to ensure their safety and efficacy in clinical applications.

2.3.5. Nanocarriers in drug delivery systems for disease treatment related to SARS-CoV-2 virus

Nanocarriers are a type of delivery system used in drug delivery for the treatment of diseases related to the SARS-CoV-2 virus. They are nano-sized particles designed to encapsulate and deliver therapeutic agents, such as drugs, vaccines, or genetic material, to targeted cells or tissues [83]. Nanocarriers can be classified into several categories, including liposomes [58], polymeric nanoparticles [104], lipid nanoparticles [58], and inorganic nanoparticles [50]. These nanoscale structures are engineered to have specific properties that enable efficient drug encapsulation, protection, and controlled release [77, 83, 121]. Nanocarriers provide a protective environment for drugs or therapeutic agents, allowing them to remain stable during transportation and delivery [122]. The drugs can be encapsulated within the core of the nanocarrier or loaded onto the surface, depending on the specific design and composition of the nanocarrier. Nanocarriers can be surface-modified with targeting ligands or antibodies that selectively bind to receptors or markers on specific cells, improving the specificity and efficacy of drug delivery [123]. This targeted approach helps to increase drug concentration at the desired site, reduce off-target effects, and enhance therapeutic outcomes [122]. Nanocarriers can be designed to release the encapsulated drug in a controlled and sustained manner. This allows for

prolonged drug exposure at the target site, reducing the frequency of dosing and improving patient compliance. Nanocarriers have been utilized in the development of vaccines against SARS-CoV-2 [83]. They can encapsulate viral antigens or genetic material (such as messenger RNA) to enhance the immune response and promote vaccine efficacy [123]. Nanocarriers provide stability to the vaccine components and facilitate their uptake by immune cells, triggering a robust immune response against the virus [83]. Nanocarriers are designed to be stable in various physiological conditions and exhibit biocompatibility to minimize toxicity and adverse effects. Extensive characterization and testing are conducted to ensure the safety and efficacy of nanocarriers in drug delivery systems [122].

Nanocarriers offer several advantages in drug delivery for diseases related to the SARS-CoV-2 virus. They can enhance drug stability, improve targeted delivery to specific cells or tissues, and provide controlled release of therapeutic agents [124]. Moreover, nanocarriers have the potential to overcome biological barriers, improve drug solubility, and protect drugs from degradation, leading to enhanced therapeutic outcomes. However, thorough preclinical and clinical studies are necessary to evaluate the safety, efficacy, and long-term effects of nanocarrier-based drug delivery systems in the context of SARS-CoV-2-related diseases [124].

2.3.6. Antibody-drug conjugates (ADCs) in drug delivery systems for disease treatment related to SARS-CoV-2 virus

Antibody-drug conjugates (ADCs) are a type of drug delivery system used for disease treatment, including those related to the SARS-CoV-2 virus. ADCs combine the specificity of antibodies with the cytotoxicity of drugs, allowing for targeted delivery of potent therapeutic agents to specific cells or tissues [95]. ADCs consist of three main components: a monoclonal antibody [125], a linker [126], and a cytotoxic drug [127]. The monoclonal antibody is engineered to recognize and bind to specific antigens expressed on the surface of target cells [125]. The linker serves as a bridge between the antibody and the cytotoxic drug, and it is designed to be stable in circulation but can be selectively cleaved to release the drug within the target cells [126]. The cytotoxic drug is a potent therapeutic agent that exerts its effect upon release [127]. ADCs utilize the specificity of monoclonal antibodies to selectively deliver the cytotoxic drug to cells expressing the target antigen [128]. By specifically recognizing and binding to the target cells, ADCs minimize off-target effects and reduce damage to healthy tissues, thereby improving the therapeutic index [128]. The cytotoxic drugs carried by ADCs are designed to kill target cells upon release [127]. This targeted delivery enables higher drug concentrations at the site of action, enhancing the therapeutic efficacy against the disease [128]. ADCs can potentially overcome drug resistance and improve treatment outcomes. ADCs may have potential applications in the treatment of diseases related to the SARS-CoV-2 virus [128]. For example, they could be used to selectively deliver cytotoxic drugs to cells infected with the virus, such as those expressing specific viral antigens [127]. This targeted approach may help eliminate virus-infected cells and reduce viral load, potentially improving patient outcomes. The development of ADCs involves careful selection of target antigens, antibody engineering, linker design, and choice of cytotoxic drugs [125–127]. The development process requires extensive preclinical and clinical studies to evaluate safety, efficacy, and pharmacokinetics. Challenges in ADC development include optimizing antibody selection, achieving the appropriate drug-to-antibody ratio, managing drug stability, and minimizing off-target effects. ADCs represent a promising approach in drug delivery systems for treating diseases related to the SARS-CoV-2 virus. By combining the targeting capabilities of antibodies with the cytotoxicity of drugs, ADCs have the potential to improve the therapeutic index and enhance treatment outcomes. However, further research and clinical studies are needed to explore the specific applications and effectiveness of ADCs in the context of SARS-CoV-2-related diseases. These carrier systems are being explored and optimized to improve the efficacy and safety of drug delivery for treating diseases related to the SARS-CoV-2 virus. The choice of carrier depends on factors such as the specific therapeutic agent, the desired release profile, target specificity, and the route of administration.

3. Polymer-based hydrogels in drug delivery systems for disease treatment related to SARS-CoV-2 virus

3.1. General introduction on polymer-based hydrogels in drug delivery systems

Polymer-based hydrogels are a versatile class of materials that have garnered significant attention in the field of drug delivery systems. Composing crosslinked polymer networks, these hydrogels can absorb and retain substantial amounts of water [129] or biological fluids [45]. Their unique properties, including a high water content [130], biocompatibility [131], and tunable physical and chemical characteristics [69, 84], render them highly suitable for drug delivery applications. One of the key advantages of polymer-based hydrogels is their capability to encapsulate and release therapeutic agents in a controlled manner [132]. The hydrogel matrix can serve as a reservoir for drug molecules, shielding them from degradation and enabling sustained release over an extended period [87]. This controlled release mechanism helps maintain optimal drug concentrations at the target site, improving treatment efficacy while minimizing side effects [132].

The properties of polymer-based hydrogels can be tailored to meet specific requirements in drug delivery known as drug release rate (hydrogels can be engineered to control the rate at which drugs are released. This is crucial for achieving sustained drug delivery, ensuring that therapeutic agents are released at a controlled and steady pace over time) [45, 129], and targeted drug delivery (hydrogels can be designed to release drugs at specific target sites within the body. This can minimize systemic exposure and reduce the potential for side effects while maximizing the therapeutic effect at the desired location) [86], biocompatibility (it is essential for hydrogels to be biocompatible, meaning they do not elicit adverse reactions when in contact with biological tissues. Modifying hydrogel properties can enhance their biocompatibility) [131] and others [45]. The choice of polymers, crosslinking methods, and hydrogel formulation parameters allows for customization of characteristics such as mechanical strength, degradation rate, and responsiveness to environmental stimuli [45]. This flexibility enables the design of hydrogels with desired drug release kinetics, stability, and site-specific targeting capabilities [132]. Polymer-based hydrogels also offer the potential for combination therapies, where multiple drugs or therapeutic agents can be incorporated into the same hydrogel system. This permits simultaneous or sequential delivery of different drugs, enabling synergistic effects and personalized treatment approaches [79, 81]. Furthermore, hydrogels can be engineered to respond to external stimuli such as temperature [89], pH [86], light [92], or enzymes [133], enabling triggered drug release in response to specific physiological conditions [134]. In addition to their drug delivery applications, polymer-based hydrogels have found utility in tissue engineering [90], regenerative medicine [45], and wound healing [56]. Their biocompatibility and ability to mimic the extracellular matrix make them suitable scaffolds for cell encapsulation [77], proliferation, and differentiation [45]. Hydrogels can also be functionalized with bioactive molecules, growth factors, or signaling cues to enhance tissue regeneration and promote healing processes [45, 135].

Polymer-based hydrogels are a promising platform for drug delivery systems, especially in the current landscape with the emergence of many viruses causing serious diseases, such as the SARS-CoV-2 virus. Their tunable properties, controlled release capabilities, and compatibility with biological systems make them highly appealing for a wide range of applications in the field of medicine and others, as shown in Table 2 [45]. Ongoing research and advancements in polymer chemistry, biomaterials science, and nanotechnology are expected to further enhance the design and performance of polymer-based hydrogels for targeted and efficient drug delivery.

These applications demonstrate the versatility of polymer-based hydrogels in various industries, ranging from healthcare and agriculture to consumer products and environmental protection. Researchers continue to explore new uses and innovations for hydrogel materials in diverse fields.

3.2. Classifications of polymer-based hydrogels in drug delivery systems and for disease treatment related to SARS-CoV-2 virus

3.2.1. General classifications of polymer-based hydrogels

Polymer-based hydrogels can be classified based on several criteria, including based on origin, composition, ionic charge, pore size, physical appearance, configuration, crosslinking, external stimuli response, and others [45], as shown in Figure 5.

Table 2. Applications of polymer-based hydrogels.

Fields of applications	Descriptions
Drug delivery systems	Hydrogels are widely used as drug carriers. They can encapsulate drugs and release them slowly, providing controlled drug delivery. This is valuable in the treatment of various diseases, including cancer, diabetes, and infections [45, 86].
Wound dressings	Hydrogels are used in wound care products. They create a moist environment that supports wound healing and can be loaded with antimicrobial agents to prevent infections [45].
Tissue engineering	Hydrogels are used to create scaffolds for tissue engineering. They can mimic the extracellular matrix and provide mechanical support for growing tissues and organs [90].
Contact lenses	Soft contact lenses are often made from hydrogel materials because they are comfortable to wear and allow oxygen to reach the eye [45].
Disposable diapers and sanitary products	The absorbent cores of diapers and sanitary napkins often contain hydrogel materials to absorb and retain moisture [45].
Agricultural water containing materials	Hydrogels can be used in agriculture to improve soil water retention. They can release water slowly to provide a steady source of hydration for plants [130].
Food industry	In the food industry, hydrogels can be used to encapsulate flavors, colors, and nutrients for controlled release in food products [72].
Cosmetics	Hydrogels are used in cosmetics for skincare products such as face masks and moisturizers. They provide hydration and help deliver active ingredients to the skin [136].
Biosensors	Hydrogels can be incorporated into biosensors to detect specific molecules or analytes. When the target molecule binds to the hydrogel, it can lead to a measurable signal change [75].
Artificial cartilage	Hydrogels are investigated for use as artificial cartilage due to their similarity to natural cartilage in terms of water content and mechanical properties [84].
Drug screening	Hydrogels can be used in high-throughput drug screening assays to test the effects of various compounds on cells embedded in the hydrogel [45].
Water purification	Hydrogels can be used for water purification by adsorbing pollutants and contaminants from water sources [137].
Environmental remediation	Hydrogels can be employed in environmental applications to capture and remove pollutants from soil and water [130].
Art conservation	Hydrogels can be used for the cleaning and restoration of art and cultural artifacts [45].

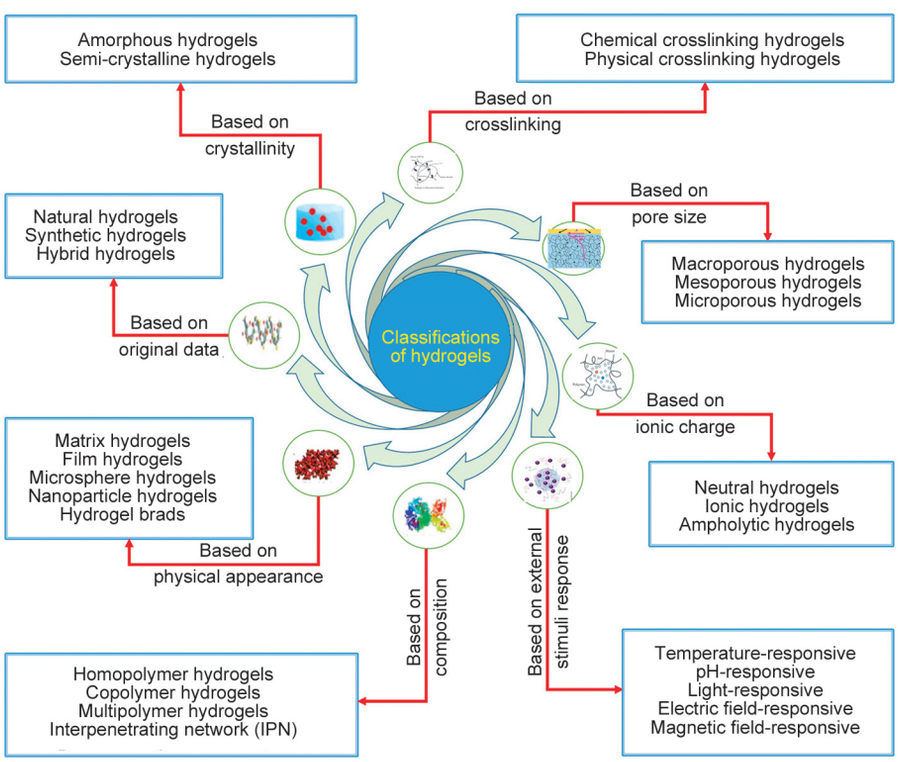

Figure 5. General classifications of polymer-based hydrogels.

Hydrogels can be classified based on their origin, such as natural hydrogels [57] (derived from natural polymers like collagen [138], alginate [139], chitosan [88]) or synthetic hydrogels [82] (created from synthetic polymers like polyethylene glycol [52], polyvinyl alcohol [85], polyacrylamide [80]). Hydrogels can be classified based on their polymer composition, such as homopolymer hydrogels [45], copolymer hydrogels [112], multipolymer hydrogels [140], and interpenetrating network hydrogels [141]. Hydrogels can be classified as cationic [142], anionic [86], or neutral based on the presence of charged groups in their polymer structure [143]. The charge of hydrogels can influence their interactions with drugs, cells, or tissues. Hydrogels can be categorized based on their pore size, which determines their permeability and ability to accommodate different-sized molecules or cells. This classification includes macroporous hydrogels [144], mesoporous hydrogels [145], and microporous hydrogels [146]. Hydrogels can be classified based on their physical appearance, such as transparent hydrogels [147], opaque hydrogels, or hydrogel films [45]. Hydrogels can be classified based on their configuration, including hydrogel nanoparticles [148], hydrogel beads [149], hydrogel microspheres [105], hydrogel fibers [92], or hydrogel membranes [45]. Hydrogels can be classified based on their crosslinking method, including physically crosslinked hydrogels (formed by physical interactions such as hydrogen bonding or physical entanglements) [150] or chemically cross-linked hydrogels (formed by covalent bonds) [151]. Hydrogels can be classified based on their responsiveness to external stimuli such as temperature, pH, light, electric fields, or magnetic fields. These include thermoresponsive hydrogels, pH-responsive hydrogels, light-responsive hydrogels, and others [45].

These are some of the common classifications of hydrogels. Each classification provides valuable information about the properties and behavior of hydrogels, allowing researchers to select the most suitable hydrogel for specific drug delivery applications and disease treatment related to the SARS-CoV-2 virus.

3.2.2. Classifications of polymer-based hydrogels in drug delivery systems for disease treatment related to SARS-CoV-2 virus

This study introduces a novel classification of polymer-based hydrogels in drug delivery for the treatment of diseases associated with the SARS-CoV-2 virus. These classifications encompass antiviral-loaded hydrogels [152], vaccines delivery hydrogels [153], targeted drug delivery hydrogels [45], inhalable hydrogels [114], personal protective equipment (PPE) hydrogels [154], and diagnostic hydrogels [155] as depicted in Figure 6. It is important to note that these classifications are not mutually exclusive, and

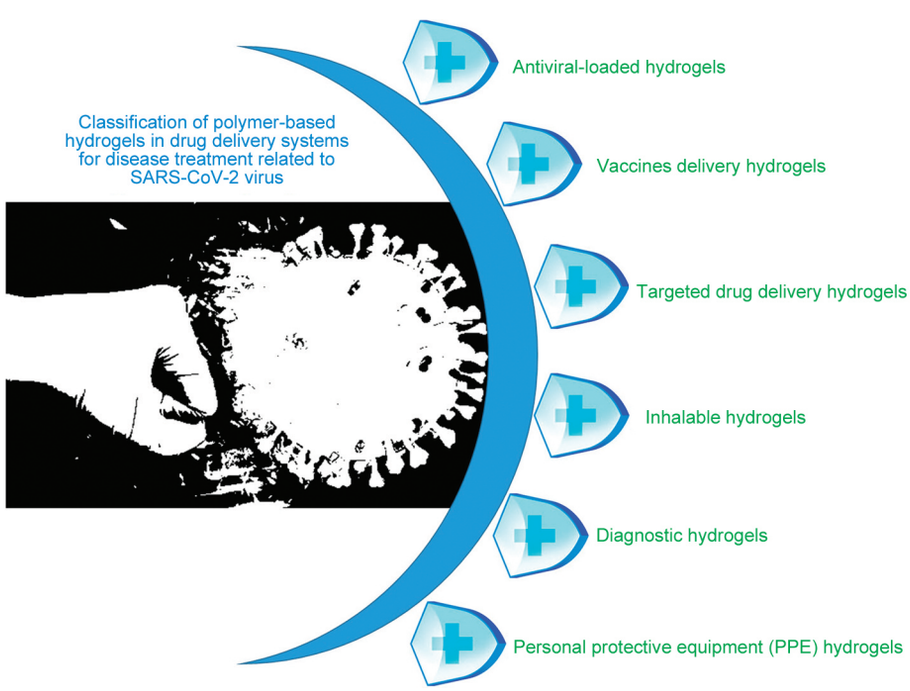

Figure 6. A novel specific classification of polymer-based hydrogels in drug delivery for treatment diseases associated with the SARS-CoV-2 virus.

hydrogels can fall into multiple categories depending on their composition, functionalization, and intended application concerning SARS-CoV-2-related diseases. The choice of hydrogel classification is contingent on the specific therapeutic objectives and requirements for effective drug delivery, treatment, or diagnostics.

Antiviral-loaded hydrogels

Antiviral-loaded hydrogels represent a specialized type of drug delivery system designed for administering antiviral agents to treat diseases associated with the SARS-CoV-2 virus. These hydrogels are formulated by integrating antiviral drugs [8] or agents into their structure, enabling controlled and sustained release of the therapeutic payload at the intended site of action [152]. The antiviral-loaded hydrogels offer several key advantages in the treatment of SARS-CoV-2-related diseases. The hydrogel matrix can be precisely engineered to target specific affected tissues [156] or organs, facilitating localized and targeted delivery of antiviral drugs [152]. This localized delivery approach serves to minimize systemic side effects and enhance therapeutic efficacy. Moreover, hydrogels enable the gradual and sustained release of antiviral agents over an extended duration [62], resulting in continuous therapeutic effects and reducing the frequency of drug administration [156]. Additionally, the hydrogel matrix acts as a protective barrier, shielding the encapsulated antiviral agents from degradation [157], enzymatic activity, or rapid clearance. This preservation of drug integrity enhances its stability and bioavailability [84]. Hydrogels can also enhance the solubility of antiviral drugs with poor water solubility [8], thereby facilitating their effective delivery and bioavailability [152].

An illustrative example of an antiviral-loaded hydrogel in the treatment of SARS-CoV-2-related diseases is the Paxlovid drug. Paxlovid, developed by Pfizer, consists of two crucial components: nirmatrelvir (chemical formula: $C_{23}H_{32}F_3N_5O_4$) and ritonavir (chemical formula: $C_{37}H_{48}N_6O_5S_2$) [8]. Nirmatrelvir functions as a potent inhibitor of the SARS-CoV-2 3C protease, a critical enzyme for preventing viral replication. Ritonavir serves as a boosting agent, enhancing the effectiveness of nirmatrelvir. Initial tests of Paxlovid against SARS-CoV-2 yielded promising results, demonstrating an 88% reduction in the risk of hospitalization and death among unvaccinated individuals [158]. Paxlovid also exhibited effectiveness against the Omicron variant. Subsequent trials, however, produced mixed outcomes. In one study involving vaccinated individuals with significant COVID-19 risk factors, Paxlovid did not show efficacy in expediting recovery from the infection in patients aged 40–64. Nevertheless, it reduced hospitalization by 73% in patients aged above 65. Clinical trial findings revealed that Paxlovid reduced the risk of hospitalization or death in high-risk patients by 89% when administered within 3 days of symptom onset and by 88% when given within 5 days [158]. The low half-maximum effective concentration (EC50) of PF-07321332 (nirmatrelvir) at 0.077 μM underscores its high potency in inhibiting the virus [158].

Antiviral-loaded hydrogels can attain a substantial drug concentration at the target site, resulting in enhanced therapeutic outcomes by effectively countering the viral infection [83]. Hydrogels offer the capability to co-encapsulate or sequentially release multiple antiviral agents, facilitating combination therapy for tackling viral infections with different mechanisms of action [157]. This approach can mitigate the risk of drug resistance and bolster treatment efficacy.

Vaccine delivery hydrogels

Vaccine delivery hydrogels represent a specialized category of drug delivery system engineered to augment the effectiveness and stability of vaccines intended for the prevention and treatment of diseases associated with the SARS-CoV-2 virus, including COVID-19. These hydrogels are meticulously designed to encapsulate or incorporate vaccines and facilitate their controlled release, precisely targeting specific sites and cells within the immune system of the body [153]. Hydrogels serve as formidable guardians, shielding vaccines from degradation and preserving their stability throughout the storage and transportation processes [8]. Within the hydrogel matrix, vaccines are safeguarded against temperature fluctuations, exposure to light, and enzymatic degradation, assuring their potency and therapeutic efficacy [153, 159]. The hydrogel formulation bestows the unique ability to orchestrate a controlled and sustained release of the vaccine antigens, closely mirroring the natural kinetics of immune response [160]. This controlled release profile holds the potential to magnify the immune response by affording prolonged exposure to the antigens, thereby fostering the development of a more resilient and enduring immune

reaction [66]. Hydrogels are adept at integrating adjuvants, substances that heighten the immune response to vaccines [153]. The adjuvants can either be co-encapsulated or conjugated within the hydrogel matrix, offering the dual advantage of reinforcing the immune response to the vaccine antigens and extending its duration [160]. The hydrogel systems can be meticulously designed to target specific immune cells or tissues, such as dendritic cells, lymph nodes, or mucosal surfaces, all of which play pivotal roles in vaccine-induced immune responses [66]. This precisely targeted delivery optimizes vaccine uptake and immune activation at the desired locale, thus fine-tuning the vaccine efficacy. Furthermore, hydrogels open up alternative routes of vaccine administration, including mucosal or transdermal delivery, obviating the need for needles [66, 153, 160]. This non-invasive approach not only enhances patient comfort but also simplifies vaccine administration, potentially streamlining large-scale vaccination initiatives. For added potency, vaccine delivery hydrogels can be synergized with other strategies, such as immune-stimulating molecules, nanoparticle systems, or physical stimuli, further amplifying the immune response and augmenting vaccine efficacy.

For example, Polysorbate 80 and Polyethylene glycol (PEG) are essential components in some COVID-19 vaccine formulations, each playing a unique role in vaccine stability and efficacy [8]. Polysorbate 80 is utilized in COVID-19 vaccines of AstraZeneca (ChAdOx1-S) [120] and Janssen (Ad26.COV2-S) to stabilize the aqueous components of the vaccine [8]. These vaccines employ a viral vector approach, encoding the SARS-CoV-2 spike glycoprotein [8]. While they have demonstrated an overall efficacy between 66.7 and 66.9%, it is important to consider that this efficacy can vary based on factors like age and the presence of new variants [8]. An interesting point to note is that vaccines containing Polysorbate 80 have been associated with fewer reported allergic reactions compared to those using PEG [8]. PEG is a key ingredient in mRNA-based COVID-19 vaccines developed by Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) [48, 110]. In these vaccines, PEG is integrated into lipid nanoparticles that stabilize the fragile mRNA molecules. These mRNA vaccines have demonstrated exceptional effectiveness in preventing COVID-19, with an effectiveness rate exceeding 94% in clinical trials for subjects between the ages of 18 and 65 [116].

The choice between Polysorbate 80 and PEG in vaccine formulations reflects various considerations. Both stabilizers serve crucial roles in maintaining the vaccine's integrity and enhancing its delivery to target cells. Reports of reduced allergic reactions with Polysorbate 80 suggest its potential advantage in terms of safety, especially for individuals prone to allergies. However, vaccine efficacy is not solely determined by these stabilizers but by the overall vaccine design, including the choice of platform, antigen, and formulation [8, 110]. Factors like age, variants of the virus, and individual immune responses also contribute to vaccine performance. The selection of Polysorbate 80 or PEG in COVID-19 vaccines is a part of the intricate process of vaccine development, with each option having its unique benefits and considerations [116]. Vaccine safety and efficacy are continually monitored and studied to ensure the best possible protection against COVID-19.

Targeted drug delivery hydrogels

Targeted drug delivery hydrogels tailored for disease treatment associated with the SARS-CoV-2 virus are meticulously engineered to transport therapeutic agents with precision to the specific cells or tissues implicated in the infection or the associated symptoms of COVID-19. For example, remdesivir is a notable drug employed in the treatment of COVID-19 pneumonia. This antiviral medication is a carboxylic ester resulting from the formal condensation of the carboxyl group of N-[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy) phosphoryl]-L-alanine with the hydroxyl group of 2-ethylbutan-1-ol [83, 161]. Remdesivir exhibits remarkable characteristics as a broad-spectrum antiviral prodrug, displaying potent *in vitro* antiviral activity against a diverse panel of RNA viruses like the SARS-CoV-2 virus [83, 161].

The hydrogels offer the distinct advantage of effecting localized and sustained drug release, thus minimizing off-target effects and significantly enhancing treatment outcomes [45, 86]. Targeted hydrogels can be adorned with specific ligands possessing a particular affinity for receptors or markers prominently present on the surface of the target cells [113]. For SARS-CoV-2, potential targets may encompass ACE2 receptors or other receptors integral to viral entry or replication processes [162]. By seamlessly integrating these targeting ligands, the hydrogels become

proficient in selectively binding to and transporting drugs solely to the cells directly implicated in the infection. The hydrogel matrix orchestrates a meticulously controlled release of therapeutic agents, guaranteeing a sustained and localized drug delivery to the designated target site [45, 86, 162]. This measured release profile not only amplifies therapeutic efficacy but also effectively mitigates systemic side effects. Targeted drug delivery hydrogels dispense a diverse array of therapeutic agents, including antiviral drugs [8], immunomodulators [163], anti-inflammatory agents [164], and other disease-modifying agents [45]. These drugs, in turn, serve to inhibit viral replication, mitigate inflammation, regulate the immune response, or target specific disease pathways related to SARS-CoV-2 infection [165]. The versatility of these targeted hydrogels allows for the simultaneous or sequential delivery of multiple drugs, thereby enabling combination therapy [8, 163]. This multifaceted approach significantly enhances treatment effectiveness by addressing several disease mechanisms or pathways concurrently, a pivotal consideration given the intricate nature of SARS-CoV-2 infection. The hydrogel-based drug delivery systems can be administered directly to the affected tissues or organs, such as the respiratory tract or lungs, which represent the primary sites of SARS-CoV-2 infection [8, 163, 165]. This localized administration substantially augments drug concentration at the target site while concurrently diminishing systemic exposure. Certain targeted hydrogels are designed to respond to specific stimuli, such as alterations in pH, temperature, or enzyme activity, thereby initiating drug release exclusively at the target site [45]. These stimuli-responsive hydrogels are customarily tailored to dispense drugs to distinctive microenvironments associated with SARS-CoV-2 infection.

Inhalable hydrogels

Inhalable hydrogels designed for disease treatment related to the SARS-CoV-2 virus constitute a specialized class of drug delivery system engineered to deliver therapeutics directly to the respiratory system through inhalation. These hydrogels offer numerous advantages, particularly in the context of respiratory infections like COVID-19. Inhalable hydrogels are meticulously formulated to be administered as aerosols or dry powders, facilitating their inhalation into the respiratory tract [114]. This route of administration enables the targeted delivery of therapeutics directly to the lungs, which represent the primary site of SARS-CoV-2 infection and the source of respiratory symptoms [166]. By directly conveying therapeutics to the respiratory system, inhalable hydrogels facilitate localized drug delivery, thereby maximizing drug concentration precisely at the site of infection [167]. This localized approach serves to enhance the efficacy of treatment while simultaneously minimizing systemic side effects. Furthermore, inhalable hydrogels can be engineered to possess optimal particle size and properties that promote prolonged retention within the lung [168]. This prolonged residence ensures that the therapeutic agents persist within the lungs for an extended duration, thus enabling sustained release and prolonged therapeutic efficacy [114]. Hydrogels can be intentionally endowed with mucoadhesive properties, which enable them to adhere to the mucosal surfaces lining the respiratory tract [45]. This adhesion fosters prolonged contact between the hydrogel and the target tissues, thus facilitating enhanced drug absorption and bioavailability [166]. Inhalable hydrogels can also be purposefully designed to possess controlled release properties, permitting the sustained and regulated delivery of therapeutics over an extended period [167]. This controlled release profile serves to optimize drug concentration within the lungs, thereby further enhancing treatment efficacy [169]. Inhalable hydrogels can be employed to simultaneously deliver multiple therapeutics agents, thus allowing for combination therapy. This aspect proves particularly advantageous in the text of SARS-CoV-2-related diseases, as it facilitates the delivery of antiviral drugs, anti-inflammatory agents, immunomodulators, or other therapeutic agents targeting various aspects of the infection [169]. Hydrogels, when employed in the respiratory tract, can additionally serve as a protective barrier, creating a physical blockade against pathogens and thereby reducing the risk of infection or transmission. Furthermore, they contribute to maintaining adequate moisture levels within the respiratory system, which, in turn, promotes the healing of damaged tissues.

Personal protective equipment (PPE) hydrogels

Personal protective equipment (PPE) hydrogels represent a specialized class of hydrogel materials employed in the development of protective gear and equipment aimed at preventing the transmission of diseases, including those related to the SARS-CoV-2 virus [136, 154]. These hydrogels are meticulously

engineered to augment the safety and effectiveness of PPE by integrating unique properties and functionalities [137]. PPE hydrogels are strategically crafted to serve as a physical barrier that impedes the transmission of pathogens, encompassing viruses like SARS-CoV-2 [154]. The hydrogel material functions as a protective layer, obstructing the passage of microorganisms, respiratory droplets, and other contaminants, thereby reducing the risk of infection [170]. Hydrogels used in PPE are often formulated to be lightweight, flexible, and comfortable to wear [137, 170]. They readily conform to the body contours and provide a breathable environment, ensuring that individuals can wear them for extended periods without discomfort [154]. PPE hydrogels may incorporate moisture-absorbing or moisture-wicking properties [170], effectively managing perspiration and moisture accumulation within the protective gear. This feature keeps the wearer dry and comfortable during prolonged use [136]. Certain PPE hydrogels may also integrate antimicrobial agents or be engineered to possess inherent antimicrobial properties, thereby inhibiting the growth and proliferation of bacteria and viruses, including SARS-CoV-2, on the surface of the protective equipment [170]. Hydrogels employed in PPE can be designed to be reusable and durable, enabling multiple uses without compromising their protective properties [154]. They are capable of withstanding repeated disinfection and cleaning processes, ensuring that the PPE retains its effectiveness over time. Importantly, PPE hydrogels are typically engineered to be biocompatible, meaning they are non-toxic and safe for skin contact [136]. This feature is crucial in preventing allergic reactions or adverse skin responses when individuals don the protective gear. Hydrogels offer remarkable versatility in terms of their formulation and fabrication, facilitating customization to suit specific PPE requirements. They can be tailored to various shapes, sizes, and functionalities, all contingent upon the intended use and level of protection necessitated.

Diagnostic hydrogels

Diagnostic hydrogels play a pivotal role in the management and treatment of diseases, including those linked to the SARS-CoV-2 virus. These hydrogels are meticulously designed to detect infections, monitor disease progression, and furnish critical information for healthcare professionals [155]. Hydrogels can be functionalized with specific probes, such as DNA or RNA sequences, antibodies, or antigens, to identify viral genetic material or specific biomarkers associated with SARS-CoV-2 infection [142, 143]. These hydrogels are adaptable to various diagnostic techniques, including polymerase chain reaction (PCR) [139], loop-mediated isothermal amplification (LAMP) [171, 172], or nucleic acid hybridization assays [155]. They can also be engineered to capture and detect viral antigens, like the spike protein or nucleocapsid protein of SARS-CoV-2. Frequently, these hydrogels are coupled with immunological assays such as enzyme-linked immunosorbent assays (ELISA), lateral flow assays, or immunofluorescence assays, enabling rapid and precise detection of viral antigens in patient samples [45, 155, 171–173]. Hydrogels serve as sensitive platforms in biosensors for the detection of viral particles or biomarkers [174]. By incorporating specific receptors or functional groups into the hydrogel matrix, they selectively bind to target molecules, generating a measurable signal. This encompasses optical sensors, electrochemical sensors, or microfluidic-based sensors, facilitating the rapid and sensitive detection of SARS-CoV-2-related analytes [173, 174]. Hydrogels can be integrated into portable or handheld diagnostic devices for point-of-care testing. These devices often employed miniaturized hydrogel-based assays, microfluidics, or lab-on-a-chip technologies to provide swift and sensitive detection of viral infections [174]. Point-of-care testing ensures immediate results, expedites early diagnosis, and supports prompt treatment decisions. Moreover, hydrogels can be functionalized with imaging agents such as fluorescent dyes, nanoparticles, or magnetic resonance imaging (MRI) contrast agents, enabling visualization of viral infections or specific biomarkers associated with SARS-CoV-2 [45, 174]. These hydrogel-based imaging agents yield valuable information for disease staging, treatment monitoring, and disease progression assessment.

3.3. Novel products of polymer-based hydrogels from recent research in drug delivery systems for disease treatment related to SARS-CoV-2 virus

Numerous research reports have delved into the development and application of hydrogels in drug delivery for the treatment of the disease related to the

SARS-CoV-2 virus over the years. Table 3 summarizes previous published contents related to using polymer-based hydrogels applied in drug delivery. This section aims to provide an up-to-date evaluation of recent innovations in polymer-based hydrogel products for drug infusion in the treatment of SARS-CoV-2-related diseases, focusing on developments in the early months of 2023. It is worth noting that these recent findings have only been disseminated through individual publications by various research groups, lacking comprehensive analyses and evaluation of these emerging hydrogel technologies.

Table 3. Summary of recent publications on polymer-based hydrogels for drug delivery.

References	Descriptions
Hillary and Ceasar [8]	The article provided a concise summary of the evolving dynamics of SARS-CoV-2 transmission, the emergence of significant SARS-CoV-2 variants (including both variants of concern and variants of interest), and offers a brief overview of the antiviral medications and vaccines being employed in the fight against SARS-CoV-2.
Thang *et al.* [45]	This article distinguished itself by introducing fresh perspectives and innovations in the realm of polymer-based hydrogels for drug delivery systems. It extended the existing knowledge base by presenting inventive concepts, methodologies, and applications that drive progress in this field. These innovations held promise for improving the effectiveness, safety, and patient adherence of drug delivery systems, ushering in modern advancements in biomedical materials.
Murray *et al.* [47]	The authors conducted a review that examines the influence of pre-existing humoral and T cell immune responses on SARS-CoV-2 infection and vaccination outcomes. They also explored the significance of conserved coronavirus epitopes in designing broad-spectrum coronavirus vaccines. Additionally, the authors assessed how immune responses cross-react between the original SARS-CoV-2 virus and its variants and their implications for COVID-19 vaccination.
Ratajczak *et al.* [48]	This research aimed to evaluate the efficacy and safety of tozinameran (30 µg, BNT162b2, Pfizer, BioNTech) and elasomeran (100 µg, mRNA-1273, Moderna) in preventing COVID-19 in individuals aged 16 years and older who received two doses of these vaccines. Both BNT162b2 and mRNA-1273 vaccines demonstrated significant effectiveness in preventing COVID-19 compared to a placebo (Mantel-Haenszel [MH], RR 0.08 [0.07, 0.09], $p < 0.00001$, 95% CI). However, the administration of these vaccines was associated with a higher incidence of adverse events compared to the placebo (Inverse Variance [IV], RR 2.14 [1.99, 2.29], $p < 0.00001$, 95% CI). Notably, the occurrence of serious adverse events did not significantly differ between the vaccines and placebo (MH, RR 0.98 [0.89, 1.08], $p = 0.68$, 95% CI). Conclusions: Tozinameran and elasomeran have demonstrated both efficacy and safety in preventing COVID-19.
Zeedan *et al.* [49]	The article provided insights into adenovirus vector (Ad vector) vaccines for SARS-CoV-2 in humans and addressed concerns related to Ad vector-induced hemagglutination. Comparing the effectiveness of various COVID-19 vaccines is challenging due to differences in phases of clinical trials assessing safety, dosage schedules, and individual protection levels. These vaccines demonstrated a wide range of protection, with Pfizer and BioNTech's vaccine showing 80 to 95% efficacy and AstraZeneca's vaccine from Oxford revealing approximately 60 to 70% efficacy. Importantly, the adenovirus-based ChAdOx1 nCoV-19 and mRNA-based BNT162b2 and mRNA-1273 vaccines maintained their effectiveness even in the presence of SARS-CoV-2 variants like alpha, beta, gamma, and delta, underlining their robustness.
Far *et al.*, [148]	The authors discussed the use of hydrogels as drug delivery systems for HCC (Hepatocellular Carcinoma) and covered various types of hydrogels, including thermosensitive, pH-sensitive, photosensitive, dual-sensitive, and glutathione-responsive hydrogels. Hydrogel-based drug delivery methods have shown superior effectiveness in treating cancer compared to conventional systemic chemotherapy.
Wang *et al.* [149]	In this study, CMCS-CuO nanoparticles were incorporated into the SA matrix through a blending method, resulting in the formation of SA/CMCS-CuO composite microspheres. Molecular interactions between CMCS-CuO NPs and the SA matrix were confirmed. Swelling experiments indicated that increasing the mass of CMCS-CuO NPs led to a reduction in the maximum swelling ratio of the gel microspheres, decreasing from 49.83 to 38.2%, and extending the time required to reach the maximum swelling ratio from 8 to 11 hours. A series of tests demonstrated the excellent biocompatibility of the composite microspheres. Subsequently, curcumin was blended with the composite bead matrix, and curcumin-loaded SA/CMCS-CuO composite beads were produced using the crosslinking method. *In vitro* release experiments highlighted the pH sensitivity of SA/CMCS-CuO composite microspheres, with the inclusion of CMCS-CuO NPs prolonging the *in vitro* release time of curcumin. These findings suggest that these microspheres hold potential for drug delivery applications.
Kallem *et al.* [137]	In this paper, the authors assessed and elucidated the most recent advancements in quantifying, detecting, and inactivating SARS-CoV-2 in wastewater. Also, they discussed the limitations of these methods and provided recommendations for future research in this field.
Patil *et al.* [175]	The article introduced diverse applications of microfluidic systems for precisely synthesizing organic and inorganic nanoparticles with controlled sizes. It discussed micromixers and their recent developments in drug delivery systems. The authors reviewed the crucial role of spray and freeze-drying in nanoparticle production. Furthermore, the paper emphasizes the concept and compares a microreactor-assisted spray and freeze dryer for creating an innovative drug delivery platform. Finally, the paper presented and discussed various recent patents related to microfluidics and applicable drying technologies.

Table 3. Continuosly

References	Descriptions
Zhang *et al.* [116]	The authors conducted an assessment of the effectiveness of mRNA and viral-vector vaccines during the epidemic period caused by various SARS-CoV-2 variants. They performed a systematic search of PubMed, EMBASE, and CNKI (China National Knowledge Infra-structure) databases, without language restrictions, for studies published before September 19, 2022. The overall vaccine effectiveness (VE) in preventing COVID-19 infection was 0.76 (95% confidence interval [CI] 0.73–0.78), while for symptomatic infection, it was 0.87 (95% CI 0.83–0.91). VE against hospital admissions was 0.82 (95% CI 0.75–0.87), and for mortality, it was 0.76 (95% CI 0.48–0.89). Subgroup analyses were performed to characterize the effectiveness of different vaccines. When considering SARS-CoV-2 variants, VE exhibited a decrease in association with virus variations across clinical outcomes and vaccine types. The findings from this systematic review suggested that BNT162b2, mRNA-1273, ChAdOx1, and Ad26.COV2.S vaccines appeared to be reasonably effective from the pre-delta to omicron variants but showed only modest effectiveness in participants aged 65 or older. When accounting for SARS-CoV-2 variants, VE decreased in correlation with virus variations for all mRNA and viral-vector vaccines.
Sandoval *et al.* [117]	The authors conducted an evaluation of the efficacy, immunogenicity, and safety of mRNA, protein subunit, or viral vector vaccines against SARS-CoV-2 in adults over 18 years old, with a specific focus on assessing the timing of COVID-19 vaccinations. The results indicated that the new vaccines exhibited over 90% efficacy against SARS-CoV-2, regardless of the technology used. Additionally, adverse reactions were generally mild to moderate, and all vaccine types displayed good immunogenicity.

3.3.1. A novel inhibitor of Aphe-NP14

Li *et al.* [62] reported introduced a novel inhibitor named Aphe-NP14. The synthesis of bio-tinylated Aphe-NP14 involved several steps. A monomer mixture consisting of 58% Aphe (*N*-acryloyl-L-phenylalanine in 1 mL ethanol), 38% *N*-tert-butylacrylamide (in 1 mL ethanol), 2% crosslinking agent (BIS), and 2% *N*-(3-methacrylamidopropyl)-D-biotinamide (BIO) was dissolved in water containing 10 mg of sodium dodecyl sulfate. This resulted in a total monomer concentration of 32.5 mM within a total volume of 25 mL [62]. The procedures for synthesizing, purifying, and characterizing biotinylated Aphe-NP14 were consistent with those used for polymer NPs that did not contain BIO [62].

Aphe-NP14 is a synthetic hydrogel polymer nanoparticle meticulously designed to target specific residues within the receptor binding domain (RBD) of the SARS-CoV-2 spike glycoprotein, which is crucial for binding to the human angiotensin-converting enzyme 2 (ACE2). This hydrogel nanoparticle library was created by incorporating monomers with functionalities that align with these critical residues. Aphe-NP14 boasts several advantageous properties that render it a potent inhibitor against SARS-CoV-2 and its variants. It possesses a remarkable spike in RBD adsorption capacity, enabling it to bind to the viral protein effectively. Furthermore, it exhibits rapid adsorption kinetics, signifying its swift binding to the target. The inhibitor showcases strong affinity, ensuring a robust interaction with the spike RBD. Notably, it demonstrates a broad specificity, effectively neutralizing not only the wild-type SARS-CoV-2 but also the current variants of concern, including Beta, Delta, and Omicron spike RBD [62].

The internalization of Aphe-NP14 by the spike RBD leads to the blockage of the spike RBD-ACE2 interaction, a pivotal step in viral entry into host cells. Consequently, Aphe-NP14 demonstrates potent neutralization efficacy against the variant pseudo typed viruses, effectively impeding their capacity to infect host cells [62]. Moreover, it exhibits inhibitory effects on live SARS-CoV-2 virus recognition, entry, replication, and infection both *in vitro* and *in vivo*, underscoring its potential as a preventive and therapeutic agent. Importantly, Aphe-NP14 has demonstrated safety for intranasal administration, showing low toxicity in both *in vitro* and *in vivo* studies. This favorable safety profile holds significant promise for its potential application in the prevention and treatment of SARS-CoV-2 infection, including emerging variants [62]. These findings suggest that synthetic antibody inhibitors like Aphe-NP14 hold substantial potential in combating current and future variants of SARS-CoV-2 and may contribute significantly to developing effective strategies for preventing and treating COVID-19.

3.3.2. A novel nanosuspension of Remdesivir based on solubilizing polymers, poloxamer 407, and β-cyclodextrin

In a study by Mehmood *et al.* [161], a groundbreaking nanosuspension of Remdesivir, an antiviral drug with potential against SARS-CoV-2, was developed. The primary objective was to overcome the significant challenge of poor aqueous solubility of Remdesivir,

which limits its therapeutic effectiveness. To address this issue, the researchers focused on nasal delivery and employed solubilizing polymers, specifically poloxamer 407, and β-cyclodextrin [161]. The formulation of this nanosuspension resulted in a remarkable enhancement in the solubility of Remdesivir. Additionally, the study explored pulmonary delivery for the first time to enhance the *in vivo* performance of the drug. By encapsulating Remdesivir at the nanoscale using polymers of Poloxamer 407 and β-cyclodextrin, both its solubility and biocompatibility were significantly improved. Here, Poloxamer 407 is a hydrophilic non-ionic surfactant belonging to the broader class of copolymers. It comprises a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol (PEG) [161]. On the other hand, β-cyclodextrin, often abbreviated as β-CD, is a heptasaccharide derived from glucose, appearing as a white (colorless) powder or crystals with excellent solubility in PEG, which helps reduce the production cost of the final product [161]. The nanosuspension was meticulously prepared using a modified precipitation-ultrasonication process and exhibited highly desirable characteristics. The particle size measured approximately 500 nm with a low polydispersity index (0.226±0.02), and the zeta potential was –16.0±2 mV, indicating excellent stability [161]. Furthermore, characterization studies such as XRD and DSC the conversion of Remdesivir crystals into an amorphous form. Morphological analysis using SEM revealed that the nanoparticles had a spherical and uniform shape. Compatibility between the drug and polymers was validated through FTIR studies.

The study also included comprehensive toxicity investigations, encompassing hemolysis and MTT assay, which consistently indicated the biocompatibility of the nanosuspension. Moreover, histopathology studies on goat nasal mucosa revealed no adverse effects on the nasal tissues. Notably, the researchers delved into the anti-inflammatory effects of the nanosuspension, and reverse transcription polymerase chain reaction (RT-PCR) analysis showed reduced levels of IL-4 mRNA expression, suggesting a decrease in pro-inflammatory cytokines [117]. In comparison to intravenous delivery, nasal administration of the Remdesivir nanosuspension offers numerous advantages, including ease of use and enhanced patient compliance. The study underscores the potential of delivering Remdesivir via the nasal route using a well-developed nanosuspension formulation, presenting a promising approach for the treatment of SARS-CoV-2 infections.

3.3.3. A new electrochemical sensor for the detection of the SARS-CoV-2 spike protein (S protein)

Chen *et al.* [91] conducted a study aimed at developing an innovative electrochemical sensor using poly-*N*-isopropylacrylamide microgels for the sensitive detection of the SARS-CoV-2 spike protein (S protein) in human saliva. The microgel employed in this sensor was constructed from a copolymer consisting of *N*-isopropylacrylamide and acrylic acid, and it incorporated gold nanoparticles within the microgel structure using a straightforward and cost-effective fabrication process, as shown in Figure 7. The electrochemical performance of this sensor was meticulously evaluated via differential pulse voltammetry. Under optimal experimental conditions, the sensor demonstrated a linear range of 10^{-13} to 10^{-9} mg/mL for the S protein, boasting an impressive

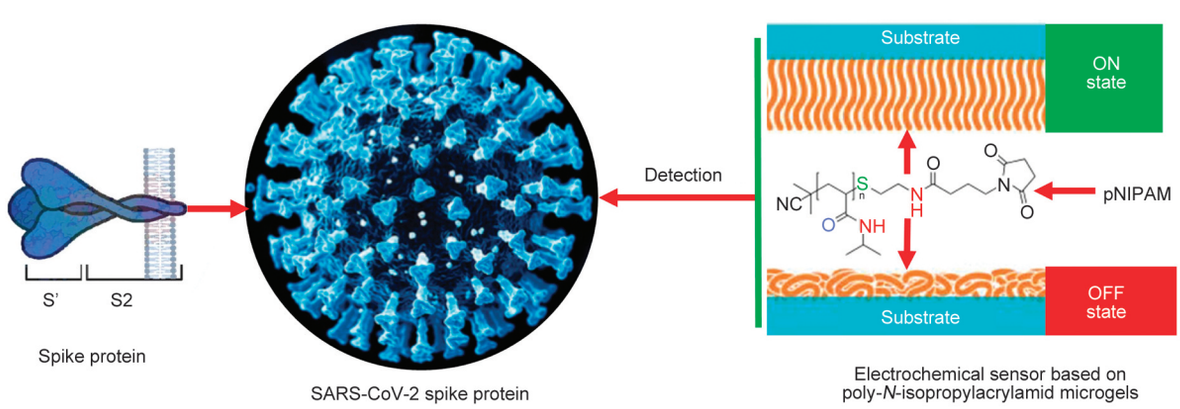

Figure 7. Fabrication of electrochemical sensor using poly-*N*-isopropyl acrylamide microgels for the sensitive detection of the SARS-CoV-2 spike protein (S protein) in human saliva.

detection limit of 9.55 fg/mL [91]. To mimic infected human saliva, the researchers introduced the S protein into an artificial saliva matrix, and the sensing platform consistently exhibited reliable detection capability within this model. The developed sensor showcased exceptional specificity and sensitivity when detecting the spike protein, underscoring its potential for rapid and cost-effective identification of SARS-CoV-2. This pioneering sensing platform holds significant promise in the realm of diagnostics, presenting a valuable tool for the timely and accurate detection of SARS-CoV-2 infections.

3.4. Expectations and challenges of polymer-based hydrogels in drug delivery for treatment related to SARS-CoV-2 virus in the future

3.4.1. Expectations of polymer-based hydrogels in drug delivery for treatment related to SARS-CoV-2 virus in the future

Polymer-based hydrogels stand poised for significant advancements in the field of drug delivery for the treatment of the disease related to the SARS-CoV-2 virus. In the future, humans can anticipate several notable improvements in the utilization of these hydrogels, including:

Enhanced targeting and specificity

Researchers are poised to develop polymer-based hydrogels with superior targeting capabilities, enabling precise delivery of therapeutics to specific tissues or cells implicated in SARS-CoV-2 infection. This precision could maximize therapeutic effectiveness while minimizing off-target effects.

Stimuli-responsive release systems

Future hydrogel formulations may incorporate sophisticated stimuli-responsive mechanisms, such as pH, temperature, or enzyme triggers, enabling on-demand and controlled drug release. This flexibility would allow tailored drug delivery profiles, optimizing treatment outcomes.

Combination therapies

Polymer-based hydrogels can facilitate the simultaneous delivery of multiple drugs or therapeutic agents. In the future, we may witness the development of hydrogel systems that enable combination therapies, encompassing antiviral drugs, immunomodulators, and other therapeutics, to target multiple faces of SARS-CoV-2 infection and enhance treatment effectiveness.

Long-acting formulations

Extended-release formulations of polymer-based hydrogels have the potential to provide sustained drug release over an extended duration. This could reduce the frequency of administration, thereby enhancing patient compliance. Such formulations could be particularly advantageous for prophylactic treatments or long-term management of SARS-CoV-2-related conditions.

Personalized medicine

As precision medicine continues to advance, polymer-based hydrogels might play a pivotal role in personalized drug delivery systems. By tailoring hydrogel properties to individual patient characteristics, such as disease severity, genetic profile, or immune response, more effective and personalized treatment strategies can emerge.

Advanced characterization techniques

In step with evolving analytical techniques, we can anticipate the development of advanced characterization methods for polymer-based hydrogels. These techniques will offer valuable insights into structural properties, drug release kinetics, and interactions within the hydrogel matrix, empowering researchers to optimize their design and performance.

Regulatory approvals and commercialization

Bolstered by promising preclinical and clinical research outcomes, certain polymer-based hydrogel drug delivery systems are likely to advance through regulatory approvals and enter the commercial market for SARS-CoV-2-related treatments. This development will increase accessibility to these innovative therapies on a global scale.

The future of polymer-based hydrogels in drug delivery for SARS-CoV-2-related diseases brims with potential, spanning advancements in targeted delivery, sustained release, combination therapies, and personalized medicine. Ongoing research and collaboration among scientists, clinicians, and industry partners will be pivotal in translating these prospects into tangible progress and improving patient outcomes.

3.4.2. Challenges of polymer-based hydrogels in drug delivery for treatment related to SARS-CoV-2 virus in the future

In the future, the utilization of polymer-based hydrogels in drug delivery for treating diseases linked to the SARS-CoV-2 virus may still encounter specific challenges.

Variability of SARS-CoV-2 variants

As novel SARS-CoV-2 variants continue to surface, there might be challenges concerning the effectiveness of drug delivery systems, including polymer-based hydrogels, against these variants. Thorough investigations are essential to ascertain the hydrogel's ability to precisely target and neutralize various variants to sustain therapeutic efficacy.

Vaccine delivery

Polymer-based hydrogels exhibit potential for vaccine delivery systems. However, hurdles may arise concerning vaccine stability and long-term storage within the hydrogel matrix. Developing hydrogels capable of safeguarding and delivering vaccines while preserving their potency and immunogenicity will be pivotal for future vaccine delivery strategies.

Immunogenicity and safety concerns

The long-term immunogenicity and safety of polymer-based hydrogels used in SARS-CoV-2 drug delivery warrant careful evaluation. Certain hydrogel formulations might trigger immune responses or provoke adverse reactions in patients. Hence, extensive preclinical and clinical investigations are necessary to ensure their safety and minimize potential risks.

Systemic delivery challenges

While many drug delivery systems emphasize localized delivery, there may be a demand for systemic therapeutics delivery to combat systemic SARS-CoV-2 manifestations effectively. Overcoming challenges associated with the biodistribution, clearance, and targeting of hydrogel-based drug delivery systems in systemic circulation will be pivotal for their success in addressing the virus's systemic aspects.

Manufacturing and scalability

Scaling up the production of polymer-based hydrogels with consistent quality and reproducibility remains a challenge. The development of robust, cost-effective manufacturing processes for large-scale production while retaining the desired properties and performance of hydrogels is crucial for their widespread adoption.

Regulatory approval

Securing regulatory approval for polymer-based hydrogel drug delivery systems tailored to SARS-CoV-2-related treatments might necessitate comprehensive preclinical and clinical studies. Meeting regulatory standards concerning safety, efficacy, quality, and manufacturing processes is imperative for their successful integration into clinical practice.

Addressing these challenges will demand continuous research, collaboration, and innovation in the field of polymer-based hydrogels. Close cooperation among researchers, clinicians, regulatory bodies, and industry stakeholders will be harnessing the potential of polymer-based hydrogels for effective drug delivery in the treatment of diseases related to the SARS-CoV-2 virus in the future.

3.5. Future directions of polymer-based hydrogels in drug delivery for treatment related to SARS-CoV-2 virus

As research on polymer-based hydrogels for drug delivery in SARS-CoV-2-related diseases continues to progress, several promising avenues for future exploration are becoming evident:

Advanced stimuli-responsive hydrogels

Developing hydrogels that respond to a broader range of stimuli, such as specific biomarkers or external triggers, could revolutionize drug delivery precision. Investigating new materials and responsive mechanisms can lead to more sophisticated systems.

Combination therapies

Research should focus on the development of hydrogel-based systems capable of delivering multiple therapeutics simultaneously. This could be especially valuable for treating emerging variants of SARS-CoV-2 or co-infections with other pathogens.

Personalized medicine

The integration of patient-specific data, such as genetic information, into hydrogel-based drug delivery systems could enable tailored treatment regimens. Customized hydrogel formulations may optimize therapeutic outcomes while minimizing side effects.

Biodegradable hydrogels
Eco-friendly and biodegradable hydrogels that break down harmlessly in the body or environment after fulfilling their drug delivery function should be explored. This aligns with the broader trend of sustainable healthcare technologies.

Real-time monitoring
Research should investigate the incorporation of biosensors or imaging agents into hydrogel systems to enable real-time monitoring of drug release and disease progression. This would facilitate adaptive treatment strategies.

Nanotechnology integration
Leveraging nanotechnology within hydrogel systems could enhance drug encapsulation efficiency and delivery precision. The design of nanoscale hydrogel carriers for targeted drug delivery warrants further attention.

Clinical translation
Bridging the gap between laboratory research and clinical applications is essential. Conducting extensive preclinical and clinical trials to validate the safety and efficacy of hydrogel-based drug delivery systems is a critical step in their adoption for patient care.

Regulatory considerations
Collaborating with regulatory agencies to establish clear guidelines for the approval and use of hydrogel-based drug delivery systems in the treatment of SARS-CoV-2-related diseases is imperative.

Global access
Ensuring equitable access to hydrogel-based therapies, particularly in low-resource settings, should be a priority. Research on cost-effective production methods and distribution networks is crucial.

Interdisciplinary collaboration
Encouraging collaboration between researchers from various fields, including materials science, pharmacology, immunology, and engineering, can yield innovative solutions to complex challenges in drug delivery for SARS-CoV-2-related diseases.
The future of polymer-based hydrogels in drug delivery for SARS-CoV-2-related diseases is promising, with numerous opportunities for innovation and improvement. By addressing these future directions, researchers can contribute to the development of more effective, personalized, and sustainable treatment strategies for the ongoing battle against viral infections like COVID-19.

4. Conclusions
Polymer-based hydrogels have emerged as promising platforms for drug delivery in the treatment of diseases related to SARS-CoV-2 virus. They possess unique properties such as high water absorption, tunable drug release, biocompatibility, and stimuli-responsiveness, which make them highly attractive for addressing the challenges posed by SARS-CoV-2 infection. Although there are obstacles to overcome, such as biocompatibility, scalability, and regulatory considerations, the future of polymer-based hydrogels in SARS-CoV-2 treatment appears promising. With ongoing research and advancements in fabrication methods, characterization techniques, and formulation strategies, significant improvements in the design and performance of polymer-based hydrogels for drug delivery are anticipated. In the future, we can expect the hydrogels to exhibit enhanced targeting capabilities, incorporate stimuli-responsive release systems, and enable the delivery of combination therapies. Personalized medicine approaches may also become more prevalent, tailoring hydrogel formulations to individual patient characteristics for optimized treatment outcomes. Furthermore, the commercialization and regulatory approval of specific polymer-based hydrogel formulations have the potential to make them widely accessible for use in SARS-CoV-2 treatment. The utilization of polymer-based hydrogels in drug delivery for SARS-CoV-2 treatment holds great promise for addressing the unique challenges posed by this viral infection. Continued research, collaboration, and innovation in this field will pave the way for more effective, patient-friendly, and targeted therapeutic interventions against SARS-CoV-2 and other infectious diseases.

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References

[1] Minervini G., Franco R., Marrapodi M. M., Mehta V., Fiorillo L., Badnjević A., Cervino G., Cicciù M.: The association between COVID-19 related anxiety, stress, depression, temporomandibular disorders, and headaches from childhood to adulthood: A systematic review. Brain Sciences, **13**, 481 (2023). https://doi.org/10.3390/brainsci13030481

[2] Roknuzzaman A. S. M., Pharm M., Sarker R., Pharm M., Nazmunnahar, Islam M. R.: The possibility and challenge evaluation about the declaration of end of the pandemic phase of Covid-19. Annals of Medicine and Surgery, **85**, 2237–2239 (2023). https://doi.org/10.1097/MS9.0000000000000569

[3] Shyamsunder, Bhatter S., Jangid K., Abidemi A., Owolabi K. M., Purohit S. D.: A new fractional mathematical model to study the impact of vaccination on COVID-19 outbreaks. Decision Analytics Journal, **6**, 100156 (2023). https://doi.org/10.1016/j.dajour.2022.100156

[4] Kaviya P., Chitra P., Selvakumar B.: A unified framework for monitoring social distancing and face mask wearing using deep learning: An approach to reduce COVID-19 risk. Procedia Computer Science, **218**, 1561–1570 (2023). https://doi.org/10.1016/j.procs.2023.01.134

[5] Tzikas A., Koulierakis G.: A systematic review of nudges on hand hygiene against the spread of COVID-19. Journal of Behavioral and Experimental Economics, **105**, 102046 (2023). https://doi.org/10.1016/j.socec.2023.102046

[6] Falck-Jones S., Österberg B., Smed-Sörensen A.: Respiratory and systemic monocytes, dendritic cells, and myeloid-derived suppressor cells in COVID-19: Implications for dis-ease severity. Journal of Internal Medicine, **293**, 130–143 (2023). https://doi.org/10.1111/joim.13559

[7] Shi H., Xu J.: The impact of COVID-19 on human body. Highlights in Science, Engineering and Technology, **36**, 1186–1192 (2023). https://doi.org/10.54097/hset.v36i.6200

[8] Hillary V. E., Ceasar S. A.: An update on COVID-19: SARS-CoV-2 variants, antiviral drugs, and vaccines. Helion, **9**, E13952 (2023). https://doi.org/10.1016/j.heliyon.2023.e13952

[9] Al-Momani H., Aolymat I., Almasri M., Mahmoud S. A., Mashal S.: Prevalence of gastro-intestinal symptoms among COVID-19 patients and the association with disease clinical outcomes. Future Science, **9**, FSO858 (2023). https://doi.org/10.2144/fsoa-2023-0040

[10] Wojtusiak J., Bagais W., Vang J., Guralnik E., Roess A., Alemi F.:The role of symptom clusters in triage of COVID-19 patients. Quality Management in Health Care, **32**, S21–S28 (2023). https://doi.org/10.1097/QMH.0000000000000399

[11] Protić A., Bura M., Šustić A., Brusić J., Sotošek V.: Segmental lung recruitment in patients with bilateral COVID-19 pneumonia complicated by acute respiratory distress syndrome: A case report. Medicina, **59**, 142 (2023). https://doi.org/10.3390/medicina59010142

[12] Hussien S. M.: The immunomodulatory properties of low-level ionizing radiation as a potential treatment for COVID-19's life-threatening symptoms. European Journal of Medical Research, **28**, 73 (2023). https://doi.org/10.1186/s40001-023-00999-7

[13] Nicolai L., Kaiser R., Stark K.: Thromboinflammation in long COVID – The elusive key to postinfection sequelae? Journal of Thrombosis and Haemostasis, **21**, 2020–2021 (2023). https://doi.org/10.1016/j.jtha.2023.04.039

[14] Regolo M., Sorce A., Vaccaro M., Colaci M., Stancanelli B., Natoli G., Motta M., Isaia I., Castelletti F., Giangreco F., Fichera D., Aparo P., Lanzafame A., Russo M., Santangelo N., Noto P., Malatino L.: Assessing humoral immuno-inflammatory pathways associated with respiratory failure in COVID-19 Patients. Journal of Clinical Medicine, **12**, 4057 (2023). https://doi.org/10.3390/jcm12124057

[15] Alessandri F., di Nardo M., Ramanathan K., Brodie D., MacLaren G.: Extracorporeal membrane oxygenation for COVID-19-related acute respiratory distress syndrome: A narrative review. Journal of Intensive Care, **11**, 5 (2023). https://doi.org/10.1186/s40560-023-00654-7

[16] Carvalho E. V., Pinto S. P. S., Gomes E. P., Peñuelas Ó., Stohler C. G., Arantes G. C., Carvalho L. L., Oliveira R. M. F., Martins P. N., Reboredo M. M., Pinheiro B. V.: Adherence to protective mechanical ventilation in COVID-19 *versus* non-COVID-19-associated acute respiratory distress syndrome: Comparison between two prospective cohorts. Medicina Intensiva, **47**, 445–453 (2023). https://doi.org/10.1016/j.medine.2023.01.004

[17] Fabbri L., Moss M., Khan F. A., Chi W., Xia J., Robinson K., Smyth A. R., Jenkins G., Stewart I.: Parenchymal lung abnormalities following hospitalisation for COVID-19 and viral pneumonitis: A systematic review and meta-analysis. Thorax, **78**, 191–201 (2023). https://doi.org/10.1136/thoraxjnl-2021-218275

[18] Lippi G., Mullier F., Favaloro E.: D-dimer: Old dogmas, new (COVID-19) tricks. Clinical Chemistry and Laboratory Medicine, **61**, 841–850 (2023). https://doi.org/10.1515/cclm-2022-0633

[19] Turner S., Khan M. A., Putrino D., Woodcock A., Kell D. B., Pretorius E.: Long COVID: Pathophysiological factors and abnormalities of coagulation. Trends in Endocrinology and Metabolism, **34**, 321–344 (2023). https://doi.org/10.1016/j.tem.2023.03.002

[20] Riazi A., Dinevari M. F., Abbasian S., Sarmadian A. J.: Upper extremity deep vein thrombosis following BBIBP-CorV COVID-19 vaccine (Sinopharm vaccine): A case report. Clinical Case Reports, **11**, e7535 (2023). https://doi.org/10.1002/ccr3.7535

[21] Rossi A. P., Donadello K., Schweiger V., Zamboni G. A., Valle Z. D., Zamboni M., Polati E., Gottin L.: Epicardial adipose tissue volume and CT-attenuation as prognostic factors for pulmonary embolism and mortality in critically ill patients affected by COVID-19. European Journal of Clinical Nutrition, **77**, 105–111 (2023). https://doi.org/10.1038/s41430-022-01197-0

[22] Hakobyan N., Ilerhunmwuwa N., Wasifuddin M., Tasnim A., Boris A.: COVID-19-associated disseminated intravascular coagulopathy presenting as inferior ST-segment elevation myocardial infarction. Cureus, **15**, e39308 (2023). https://doi.org/10.7759/cureus.39308

[23] Özdemir Ö., Şeker E., Dikici Ü., Güneş M.: Myocarditis development after COVID-19 vaccination in an immunodeficient case. Immunology Letters, **260**, 22–23 (2023). https://doi.org/10.1016/j.imlet.2023.06.001

[24] Werlein C., Ackermann M., Stark H., Shah H. R., Tzankov H., Haslbauer J. D., von Stillfried S., Bülow R. D., El-Armouche A., Kuenzel S., Robertus J. K., Reichardt M., Haverich A., Höfer A., Neubert L., Plucinski E., Braubach P., Verleden S., Salditt T., Marx N., Welte T., Bauersachs J., Kreipe H-H., Mentzer S. J., Boor P., Black S. M., Länger F., Kuehnel M., Jonigk D.: Inflammation and vascular remodeling in COVID-19 hearts. Angiogenesis, **26**, 233–248 (2023). https://doi.org/10.1007/s10456-022-09860-7

[25] Szpulak A., Garlak U., Ćwirko H., Witkowska B., Rombel-Bryzek A., Witkowska D.: SARS-CoV-2 and its impact on the cardiovascular and digestive systems – The interplay between new virus variants and human cells. Computational and Structural Biotechnology Journal, **21**, 1022–1029 (2023). https://doi.org/10.1016/j.csbj.2023.01.024

[26] Huseynov A., Akin I., Duerschmied D., Scharf R. E.: Cardiac arrhythmias in post-COVID syndrome: Prevalence, pathology, diagnosis, and treatment. Viruses, **15**, 389 (2023). https://doi.org/10.3390/v15020389

[27] El-Qushayri A. E., Dahy A., Benmelouka A. Y., Kamel A. M. A.: The effect of COVID-19 on the in-hospital outcomes of percutaneous coronary intervention in patients with acute coronary syndrome: A large scale meta-analysis. American Journal of Medicine Open, **9**, 100032 (2023). https://doi.org/10.1016/j.ajmo.2023.100032

[28] Tripathi A. K., Pilania R. K., Bhatt G. C., Atlani M., Kumar A., Malik S.: Acute kidney injury following multisystem inflammatory syndrome associated with SARS-CoV-2 infection in children: A systematic review and meta-analysis. Pediatric Nephrology, **38**, 357–370 (2023). https://doi.org/10.1007/s00467-022-05701-3

[29] Deng J., Ma Y., Liu Q., Du M., Liu M., Liu J.: Severity and outcomes of SARS-CoV-2 reinfection compared with primary infection: A systematic review and meta-analysis. International Journal of Environmental Research and Public Health, **20**, 3335 (2023). https://doi.org/10.3390/ijerph20043335

[30] Zhang Q., Jiu Y.: The regulation of host cytoskeleton during SARS-CoV-2 infection in the nervous system. Brain Science Advances, **9**, 43–52 (2023). https://doi.org/10.26599/BSA.2023.9050004

[31] Maffei M., Mazzatenta A., Origlia N.: Editorial: Loss of taste and smell in COVID-19 patients: A prognostic tool and a starting point to investigate the action of SARS-CoV-2 in the central nervous system. Frontiers in Cellular Neuroscience, **17**, 1191227 (2023). https://doi.org/10.3389/fncel.2023.1191227

[32] Caronna E., Pozo-Rosich P.: Virtual issue: COVID-19 and headache. Headache, **63**, 183–184 (2023). https://doi.org/10.1111/head.14464

[33] Aliyeva A., Han J. S., Park S. N, Olgun L.: Long-term follow-up results of tinnitus and dizziness disorders in patients after SARS-CoV-2 infection based on a questionnaire. Balkan Medical Journal, **40**, 70–71 (2023). https://doi.org/10.4274/balkanmedj.galenos.2022.2022-7-8

[34] Roe K.: SARS-CoV-2 and *Toxoplasma gondii* shared symptoms suggest muscle cells and neurons are their chronic infection reservoirs. Human Cell, **36**, 483–485 (2023). https://doi.org/10.1007/s13577-022-00809-y

[35] Narrett J. A., Mallawaarachchi I., Aldridge C. M., Assefa E. D., Patel A., Loomba J. J., Ratcliffe S., Sadan O., Monteith T., Worrall B. B., Brown D. E., Johnston K. C., Southerland A. M., N3C consortium: Increased stroke severity and mortality in patients with SARS-CoV-2 infection: An analysis from the N3C database. Journal of Stroke and Cerebrovascular Diseases, **32**, 106987 (2023). https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.106987

[36] Suzgun M. A., Kizilkilic E. K., Bostan B. U., Tutuncu M., Kızıltan G.: Parainfectious autoimmune encephalitis related to SARS-CoV-2 infection, presenting with catatonia. The International Journal of Psychiatry in Medicine, **58**, 403–410 (2023). https://doi.org/10.1177/00912174231161393

[37] Richard S. A., Pollett S. D., Fries A. C., Berjohn C. M., Maves R. C., Lalani T., Smith A. G., Mody R. M., Ganesan A., Colombo R. E., Lindholm D. A., Morris M. J., Huprikar N., Colombo C. J., Madar C., Jones M., Larson D. T., Bazan S. E., Mende K., Saunders D., Livezey J., Lanteri C. A., Scher A. I., Byrne C., Rusiecki J., Ewers E., Epsi N. J., Rozman J. S., English C., Simons M. P., Tribble D. R., Agan B. K., Burgess T. H.: Persistent COVID-19 symptoms at 6 months after onset and the role of vaccination before or after SARS-CoV-2 infection. JAMA Network Open, **6**, e2251360 (2023).
https://doi.org/10.1001/jamanetworkopen.2022.51360

[38] Bussani R., Zentilin L., Correa R., Colliva A., Silvestri F., Zacchigna S., Collesi C., Giacca M.: Persistent SARS-CoV-2 infection in patients seemingly recovered from COVID-19. The Journal of Pathology, **259**, 254–263 (2023).
https://doi.org/10.1002/path.6035

[39] Takao M., Ohira M.: Neurological post-acute sequelae of SARS-CoV-2 infection. Psychiatry Clinical Neurosciences, **77**, 72–83 (2023).
https://doi.org/10.1111/pcn.13481

[40] Nehme M., Chappuis F., Kaiser L., Assal F., Guessous I.: The prevalence, severity, and impact of post-COVID persistent fatigue, post-exertional malaise, and chronic fatigue syndrome. Journal of General Internal Medicine, **38**, 835–839 (2023).
https://doi.org/10.1007/s11606-022-07882-x

[41] Chen A., Wessler T., Forest M. G.: Antibody protection from SARS-CoV-2 respiratory tract exposure and infection. Journal of Theoretical Biology, **557**, 111334 (2023).
https://doi.org/10.1016/j.jtbi.2022.111334

[42] Rabaiotti P., Ciracì C., Donelli D., Oggioni C., Rizzi B., Savi F., Antonelli M., Rizzato M., Moderato L., Brambilla V., Ziveri V., Brambilla L., Bini M., Nouvenne A., Lazzeroni D.: Effects of multidisciplinary rehabilitation enhanced with neuropsychological treatment on post-acute SARS-CoV-2 cognitive impairment (brain fog): An observational study. Brain Sciences, **13**, 791 (2023).
https://doi.org/10.3390/brainsci13050791

[43] Marocco R., Borgo C. D., Tortellini E., Garattini S., Carraro A., di Trento D., Gasperin A., Grimaldi A., Tieghi T., Belvisi V., Kertusha B., Guardiani M., Zuccalà P., Fegatelli D. A., Spagnoli A., Lichtner M., LATINA COVID-group.: Use of Remdesivir in patients with SARS-CoV-2 pneumonia in a real-life setting during the second and third COVID-19 epidemic waves. Viruses, **15**, 947 (2023).
https://doi.org/10.3390/v15040947

[44] Metaxiotou Z., Bissig H., Batista E., do Céu Ferreira M., Timmerman A.: Metrology in health: Challenges and solutions in infusion therapy and diagnostics. Biomedical Engineering / Biomedizinische Technik, **68**, 3–12 (2023).
https://doi.org/10.1515/bmt-2022-0045

[45] Thang N. H., Chien T. B., Cuong D. X.: Polymer-based hydrogels applied in drug delivery: An overview. Gels, **9**, 523 (2023).
https://doi.org/10.3390/gels9070523

[46] Otero-Romero S., Lebrun-Frénay C., Reyes S., Amato M. P., Campins M., Farez M., Filippi M., Hacohen Y., Hemmer B., Juuti R., Magyari M., Oreja-Guevara C., Siva A., Vukusic S., Tintoré M.: European Committee for Treatment and Research in Multiple Sclerosis and European Academy of Neurology consensus on vaccination in people with multiple sclerosis: Improving immunization strategies in the era of highly active immunotherapeutic drugs. European Journal of Neurology, **30**, 2144–2176 (2023).
https://doi.org/10.1111/ene.15809

[47] Murray S. M., Ansari A. M., Frater J., Klenerman P., Dunachie S., Barnes E., Ogbe A.: The impact of pre-existing cross-reactive immunity on SARS-CoV-2 infection and vaccine responses. Nature Reviews Immunology, **23**, 304–316 (2023).
https://doi.org/10.1038/s41577-022-00809-x

[48] Ratajczak P., Banach Z., Kopciuch D., Paczkowska A., Zaprutko T., Krawczyk J., Maciuszek-Bartkowsk B., Kus K.: Tozinameran (Pfizer, BioNTech) and Elasomeran (Moderna) efficacy in COVID-19 – A systematic review of randomised controlled trial studies. Healthcare, **11**, 1532 (2023).
https://doi.org/10.3390/healthcare11111532

[49] Zeedan G. S. G., Abdalhamed A. M., Naguib A. M., Shalaby S. I. A., Awad M. A. M., Moniem M. I. A. E.: An overview of adenovirus vector-based vaccines against SARS-CoV-2. World's Veterinary Journal, **13**, 12–25 (2023).
https://doi.org/10.54203/scil.2023.wvj2

[50] Ma X., Luan Z., Li J.: Inorganic nanoparticles-based systems in biomedical applications of stem cells: Opportunities and challenges. International Journal of Nanomedicine, **18**, 143–182 (2023).
https://doi.org/10.2147/IJN.S384343

[51] Kobayashi D., Uchida H., Ishibane M., Kurita E., Kirihara M., Kotsuchibashi Y.: Fabrication of thermally cross-linked poly(methacrylic acid)-based sponges with nanolayered structures and their degradation. Polymer Journal, **55**, 163–170 (2023).
https://doi.org/10.1038/s41428-022-00721-0

[52] Koochaki A., Shahgholi M., Sajadi S. M., Babadi E., Inc M.: Investigation of the mechanical stability of polyethylene glycol hydrogel reinforced with cellulose nanofibrils for wound healing: Molecular dynamics simulation. Engineering Analysis with Boundary Elements, **151**, 1–7 (2023).
https://doi.org/10.1016/j.enganabound.2023.02.055

[53] Chang R., Chen L., Qamar M., Wen Y., Li L., Zhang J., Li X., Assadpour E., Esatbeyoglu T., Kharazmi M. S., Li Y., Jafari S. M.: The bioavailability, metabolism and microbial modulation of curcumin-loaded nanodelivery systems. Advances in Colloid and Interface Science, **318**, 102933 (2023). https://doi.org/10.1016/j.cis.2023.102933

[54] Qi X., Yuan Y., Zhang J., Bulte J. W. M., Dong W.: Oral administration of salecan-based hydrogels for controlled insulin delivery. Journal of Agricultural and Food chemistry, **66**, 10479–10489 (2018). https://doi.org/10.1021/acs.jafc.8b02879

[55] Banat H., Ambrus R., Csóka I.: Drug combinations for inhalation: Current products and future development addressing disease control and patient compliance. International Journal of Pharmaceutics, **643**, 123070 (2023). https://doi.org/10.1016/j.ijpharm.2023.123070

[56] Xu X., Zeng Y., Chen Z., Yu Y., Wang H., Lu X., Zhao J., Wang S.: Chitosan-based multifunctional hydrogel for sequential wound inflammation elimination, infection inhibition, and wound healing. International Journal of Biological Macromoleculesecules, **235**, 123847 (2023). https://doi.org/10.1016/j.ijbiomac.2023.123847

[57] Başyiğit B., Altun G., Yücetepe M., Karaaslan A., Karaaslan M.: Locust bean gum provides excellent mechanical and release attributes to soy protein-based natural hydrogels. International Journal of Biological Macromoleculesecules, **231**, 123352 (2023). https://doi.org/10.1016/j.ijbiomac.2023.123352

[58] Nel J., Elkhoury K., Velot E., Bianchi A., Acherar S., Francius G., Tamayol A., Grandemange S., Arab-Tehrany E.: Functionalized liposomes for targeted breast cancer drug delivery. Bioactive Materials, **24**, 401–437 (2023). https://doi.org/10.1016/j.bioactmat.2022.12.027

[59] Islam M. R., Rahman M. M., Dhar P. S., Nowrin F. T., Sultana N., Akter M., Rauf A., Khalil A. A., Gianoncelli A., Ribaudo G.: The role of natural and semi-synthetic compounds in ovarian cancer: Updates on mechanisms of action, current trends and perspectives. Molecules, **28**, 2070 (2023). https://doi.org/10.3390/molecules28052070

[60] Al Badri Y. N., Chaw C. S., Elkordy A. A.: Insights into asymmetric liposomes as a potential intervention for drug delivery including pulmonary nanotherapeutics. Pharmaceutics, **15**, 294 (2023). https://doi.org/10.3390/pharmaceutics15010294

[61] Mishra S., Kuru C. I., Ulucan-Karnak F.: Nanotechnology and materials science help fight against SARS-CoV-2. in 'Smart nanomaterials to combat the spread of viral infections' (eds.: Khan R., Sadique M. A.) Elsevier, Amsterdam, 295–321 (2023). https://doi.org/10.1016/B978-0-323-99148-3.00005-4

[62] Li B., Zhao Y., Wu X., Wu H., Tang W., Yu X., Mou J., Tan W., Jin M., Zhang Q., Liu M.: Abiotic synthetic antibody inhibitor with broad-spectrum neutralization and antiviral efficacy against escaping SARS-CoV-2 variants. ACS Nano, **17**, 7017–7034 (2023). https://doi.org/10.1021/acsnano.3c02050

[63] Mereness J. A., Piraino L., Chen C. Y., Moyston T., Song Y., Shubin A., DeLouise L. A., Ovitt C. E., Benoit D. S. W.: Slow hydrogel matrix degradation enhances salivary gland mimetic phenotype. Acta Biomaterialia, **166**, 187–200 (2023). https://doi.org/10.1016/j.actbio.2023.05.005

[64] Zhang R., Zhang Y., Yu J., Gao Y., Mao L.: Enhanced freeze-thawing stability of water-in-oil Pickering emulsions stabilized by ethylcellulose nanoparticles and oleogels. Carbohydrate Polymers, **312**, 120814 (2023). https://doi.org/10.1016/j.carbpol.2023.120814

[65] Lie W-R., Steiner H., Williams S., Banerjee M., Saporita A., Gilliam B., Xiao Q.: Abstract 5298: Multiplex immunoassay characterization of 48 cytokines, chemokines, and growth factors in colorectal cancer. Cancer Research, **83**, 5298 (2023). https://doi.org/10.1158/1538-7445.AM2023-5298

[66] Song H., Su Q., Nie Y., Zhang C., Huang P., Shi S., Liu Q., Wang W.: Supramolecular assembly of a trivalent peptide hydrogel vaccine for cancer immunotherapy. Acta Biomaterialia, **158**, 535–546 (2023). https://doi.org/10.1016/j.actbio.2022.12.070

[67] Du Q., Wang W., Zeng X., Luo X.: Antifouling zwitterionic peptide hydrogel based electrochemical biosensor for reliable detection of prostate specific antigen in human serum. Analytica Chimica Acta, **1239**, 340674 (2023). https://doi.org/10.1016/j.aca.2022.340674

[68] Weiss A. M., Hossainy S., Rowan S. J., Hubbell J. A., Esser-Kahn A. P.: Immunostimulatory polymers as adjuvants, immunotherapies, and delivery systems. Macromolecules, **55**, 6913−6937 (2022). https://doi.org/10.1021/acs.macromol.2c00854

[69] Park J., Lee S., Lee M., Kim H-S., Lee J. Y.: Injectable conductive hydrogels with tunable degradability as novel implantable bioelectrodes. Small, **19**, 2300250 (2023). https://doi.org/10.1002/smll.202300250

[70] Wen X., Xi K., Tang Y., Bian J., Qin Y., Xiao W., Pan T., Cheng X., Ge Z., Cui W.: Immunized microspheres engineered hydrogel membrane for reprogramming macrophage and mucosal repair. Small, **19**, 2207030 (2023). https://doi.org/10.1002/smll.202207030

[71] Yin L., Duan W., Chen Y., Chen D., Wang Y., Guo S., Qin J.: Biodegradable hydrogel from pectin and carboxymethyl cellulose with Silibinin loading for lung tumor therapy. International Journal of Biological Macromoleculesecules, **243**, 125128 (2023). https://doi.org/10.1016/j.ijbiomac.2023.125128

[72] Wang M., Yin Z., Sun W., Zhong Q., Zhang Y., Zeng M.: Microalgae play a structuring role in food: Effect of *Spirulina platensis* on the rheological, gelling characteristics, and mechanical properties of soy protein isolate hydrogel. Food Hydrocolloids, **136**, 108244 (2023). https://doi.org/10.1016/j.foodhyd.2022.108244

[73] Zhu X., Liu L., Cao W., Yuan R., Wang H.: Ultra-sensitive microRNA biosensor based on strong aggregation-induced electrochemiluminescence from bidentate ligand-stabilized copper nanoclusters in polymer hydrogel. Analytical Chemistry, **95**, 5553–5560 (2023). https://doi.org/10.1021/acs.analchem.2c04565

[74] Sharma P., Baisoya D., Chauhan D., Mishra D., Sharma M., Chandra A.: Recent progress, therapeutic concepts and pharmaceutical challenges of dendrimer based drug delivery system. Journal of Pharmaceutical Negative Results, **13**, 6865–6873 (2022). https://doi.org/10.47750/pnr.2022.13.S07.830

[75] Deshmukh R., Mishra S., Singh R.: Biosensors – A miraculous detecting tool in combating the war against COVID-19. Current Pharmaceutical Biotechnology, **24**, 1430–1448 (2023). https://doi.org/10.2174/1389201024666230102121605

[76] Li H., Li B., Lv D., Li W., Lu Y., Luo G.: Biomaterials releasing drug responsively to promote wound healing *via* regulation of pathological microenvironment. Advanced Drug Delivery Reviews, **196**, 114778 (2023). https://doi.org/10.1016/j.addr.2023.114778

[77] Ábrahám Á., Gyulai G., Tóth T., Szvoboda B., Mihály J., Szabó Á., Kiss É.: Improvement of the drug encapsulation into biodegradable polyester nanocarriers by blending of poly(lactic-*co*-glycolic acid) and polycaprolactone. Express Polymer Letters, **16**, 960–977 (2022). https://doi.org/10.3144/expresspolymlett.2022.70

[78] Liang Y., Qiao L., Qiao B., Guo B.: Conductive hydrogels for tissue repair. Chemical Science, **14**, 3091–3116 (2023). https://doi.org/10.1039/D3SC00145H

[79] Amirazad H., Khoshfetrat A. B., Zarghami N.: A dual synergistic effect of titanium and curcumin co-embedded on extracellular matrix hydrogels of decellularized bone: Potential application in osteoblastic differentiation of adipose-derived mesenchymal stem cells. Journal of Biomaterials Science, Polymer Edition, **34**, 372–397 (2023). https://doi.org/10.1080/09205063.2022.2123216

[80] Li Y., Yang D., Wu Z., Gao F-L., Gao X-Z., Zhao H-Y., Li X., Yu Z-Z.: Self-adhesive, self-healing, biocompatible and conductive polyacrylamide nanocomposite hydrogels for reliable strain and pressure sensors. Nano Energy, **109**, 108324 (2023). https://doi.org/10.1016/j.nanoen.2023.108324

[81] Bercea M., Plugariu I-A., Gradinaru L. M., Avadanei M., Doroftei F., Gradinaru V. R.: Hybrid hydrogels for neomycin delivery: Synergistic effects of natural/synthetic polymers and proteins. Polymers, **15**, 630 (2023). https://doi.org/10.3390/polym15030630

[82] Borelli A. N., Young M. W., Kirkpatrick B. E., Jaeschke M. W., Mellett S., Porter S., Blatchley M. R., Rao V. V., Sridhar B. V., Anseth K. S.: Stress relaxation and composition of hydrazone-crosslinked hybrid biopolymer-synthetic hydrogels determine spreading and secretory properties of MSCs. Advanced Healthcare Material, **11**, 2200393 (2022). https://doi.org/10.1002/adhm.202200393

[83] Jeon W-J., Lee H-K., Na Y-G., Jung M., Han S. C., Hwang J. H., Jung E., Hwang D., Shin J. S., Cho C-W.: Antiviral lipid nanocarrier loaded with Remdesivir effective against SARS-CoV-2 *in vitro* model. International Journal of Nanomedicine, **18**, 1561–1575 (2023). https://doi.org/10.2147/IJN.S391462

[84] Zhou C., Wang C., Xu K., Niu Z., Zou S., Zhang D., Qian Z., Liao J., Xie J.: Hydrogel platform with tunable stiffness based on magnetic nanoparticles crosslinked GelMA for cartilage regeneration and its intrinsic biomechanism. Bioactive Materials, **25**, 615–628 (2023). https://doi.org/10.1016/j.bioactmat.2022.07.013

[85] Khairan K., Hasan M., Idroes R., Diah M.: Fabrication and evaluation of polyvinyl alcohol/corn starch/patchouli oil hydrogel films loaded with silver nanoparticles biosynthesized in *Pogostemon cablin* benth leaves' extract. Molecules, **28**, 2020 (2023). https://doi.org/10.3390/molecules28052020

[86] Aktaş D. K., Öztekin F.: pH-Sensitive poly(acrylic acid-*co*-acrylamide) anionic hydrogels for jejunum targeted drug delivery systems. Polymer Bulletin, **80**, 2801–2813 (2023). https://doi.org/10.1007/s00289-022-04188-0

[87] Cong Y-Y., Fan B., Zhang Z-Y., Li G-Y.: Implantable sustained-release drug delivery systems: A revolution for ocular therapeutics. International Ophthalmology, **43**, 2575–2588 (2023). https://doi.org/10.1007/s10792-023-02637-x

[88] del Olmo J. A., Pérez-Álvarez L., Martínez V. S., Cid S. B., Ruiz-Rubio L., González R. P., Vilas-Vilela J. L., Alonso J. M.: Multifunctional antibacterial chitosan-based hydrogel coatings on Ti6Al4V biomaterial for biomedical implant applications. International Journal of Biological Macromolecules, **231**, 123328 (2023). https://doi.org/10.1016/j.ijbiomac.2023.123328

[89] Liu Z., Li J., Zhang Z., Liu J., Wu C., Yu Y.: Incorporating self-healing capability in temperature-sensitive hydrogels by non-covalent chitosan crosslinkers. European Polymer Journal, **182**, 111728 (2023). https://doi.org/10.1016/j.eurpolymj.2022.111728

[90] Li H., Hao Z., Zhang S., Li B., Wang Y., Wu X., Hu Y., Chen R., Chen T., Li J.: 'Smart' stimuli-responsive injectable gels for bone tissue engineering application. Macromolecular Bioscience, **23**, 2200481 (2023). https://doi.org/10.1002/mabi.202200481

[91] Chen H., Hou Z. Y., Chen D., Li T., Wang Y. M., de Lima M. A., Yang Y., Gou Z. Z.: Highly sensitive poly-*N*-isopropylacrylamide microgel-based electrochemical biosensor for the detection of SARS-COV-2 spike protein. Biomedical and Environmental Sciences, **36**, 269–278 (2023). https://doi.org/10.3967/bes2023.029

[92] Wei X., Xue Y., Sun Y., Chen L., Zhang C., Wu Q., Peng S., Ma C., Liu Z., Jiang S., Yang X., Agarwal S., Duan G.: A robust anisotropic light-responsive hydrogel for ultrafast and complex biomimetic actuation *via* poly(pyrrole)-coated electrospun nanofiber. Chemical Engineering Journal, **452**, 139373 (2023). https://doi.org/10.1016/j.cej.2022.139373

[93] Perera G. S., Rahman M. A., Blazevski A., Wood A., Walia S., Bhaskaran M., Sriram S.: Rapid conductometric detection of SARS-CoV-2 proteins and its variants using molecularly imprinted polymer nanoparticles. Advanced Materials Technologies, **8**, 2200965 (2023). https://doi.org/10.1002/admt.202200965

[94] Nguyen T. N., Phung V-D., Tran V. V.: Recent advances in conjugated polymer-based biosensors for virus detection. Biosensors, **13**, 586 (2023). https://doi.org/10.3390/bios13060586

[95] Tang W-F., Tran A-T., Wang L-Y., Horng J-T.: SARS-CoV-2 pandemics: An update of CRISPR in diagnosis and host–virus interaction studies. Biomedical Journal, **46**, 100587 (2023). https://doi.org/10.1016/j.bj.2023.02.007

[96] Malik A. H., Habib F., Qazi M. J., Ganayee M. A., Ahmad Z., Yatoo M. A: A short review article on conjugated polymers. Journal of Polymer Research, **30**, 115 (2023). https://doi.org/10.1007/s10965-023-03451-w

[97] Sharma R., Yadav S., Yadav V., Akhtar J., Katari O., Kuche K., Jain S.: Recent advances in lipid-based long-acting injectable depot formulations. Advanced Drug Delivery Reviews, **199**, 114901 (2023). https://doi.org/10.1016/j.addr.2023.114901

[98] Bangera P. D., Kara D. D., Tanvi K., Tippavajhala V. K., Rathnanand M.: Highlights on cell-penetrating peptides and polymer-lipid hybrid nanoparticle: Overview and therapeutic applications for targeted anticancer therapy. AAPS PharmSciTech, **24**, 124 (2023). https://doi.org/10.1208/s12249-023-02576-x

[99] Tang C-H., Chen H-L., Dong J-R.: Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) as food-grade nanovehicles for hydrophobic nutraceuticals or bioactives. Applied Sciences, **13**, 1726 (2023). https://doi.org/10.3390/app13031726

[100] Zeng S., Chen Y., Zhou F., Zhang T., Fan X., Chrzanowski W., Gillies M. C., Zhu L.: Recent advances and prospects for lipid-based nanoparticles as drug carriers in the treatment of human retinal diseases. Advanced Drug Delivery Reviews, **199**, 114965 (2023). https://doi.org/10.1016/j.addr.2023.114965

[101] Asr M. H., Dayani F., Segherloo S. F., Kamedi A., O'Neill A., MacLoughlin R., Doroudian M.: Lipid nanoparticles as promising carriers for mRNA vaccines for viral lung infections. Pharmaceutics, **15**, 1127 (2023). https://doi.org/10.3390/pharmaceutics15041127

[102] Kafetzis K. N., Papalamprou N., McNulty E., Thong K. X., Sato Y., Mironov A., Purohit A., Welsby P. J., Harashima H., Yu-Wai-Man C., Tagalakis A. D.: The effect of cryoprotectants and storage conditions on the transfection efficiency, stability, and safety of lipid-based nanoparticles for mRNA and DNA delivery. Advanced Healthcare Materials, **12**, 2203022 (2023). https://doi.org/10.1002/adhm.202203022

[103] Korake S., Bothiraja C., Pawar A.: Design, development, and *in-vitro*/*in-vivo* evaluation of docetaxel-loaded PEGylated solid lipid nanoparticles in prostate cancer therapy. European Journal of Pharmaceutics and Biopharmaceutics, **189**, 15–27 (2023). https://doi.org/10.1016/j.ejpb.2023.05.020

[104] da Siliva de Barros A. O., Pinto S. R., dos Reis S. R. R., Ricci-Junior E., Alencar L. M. R., Bellei N. C. J., Janini L. R. M., Maricato J. T., Rosa D. S., Santos-Oliveira R.: Polymeric nanoparticles and nanomicelles of hydroxychloroquine *co*-loaded with azithromycin potentiate anti-SARS-CoV-2 effect. Journal of Nanostructure in Chemistry, **13**, 263–281 (2023). https://doi.org/10.1007/s40097-022-00476-3

[105] Salahuddin N., Gaber M., Elneanaey S., Abdelwahab M. A.: Norfloxacin-tenoxicam dual drug delivery system based on poly(lactic acid) microspheres and electrospun fibers: Release and *in vivo* study. Express Polymer Letters, **16**, 368–387 (2022). https://doi.org/10.3144/expresspolymlett.2022.28

[106] Lysáková K., Hlináková K., Kutálková K., Chaloupková R., Žídek J., Brtníková J., Vojtová l.: A novel approach in control release monitoring of protein-based bioactive substances from injectable PLGA-PEG-PLGA hydrogel. Express Polymer Letters, **16**, 798–811 (2022). https://doi.org/10.3144/expresspolymlett.2022.59

[107] Mali A., Franci G., Zannella C., Chianese A., Anthiya S., López-Estévez A. M., Monti A., De Filippis A., Doti N., Alonso M. J., Galdiero M.: Antiviral peptides delivered by chitosan-based nanoparticles to neutralize SARS-CoV-2 and HCoV-OC43. Pharmaceutics, **15**, 1621 (2023). https://doi.org/10.3390/pharmaceutics15061621

[108] Sharifi E., Yousefiasl S., Trovato M., Sartorius R., Esmaeili Y., Goodarzi H., Ghomi M., Bigham A., Moghaddam F. D., Heidarifard M., Pourmotabed S., Zare E. N., Paiva-Santos A. C., Rabiee N., Wang X., Tay F. R.: Nanostructures for prevention, diagnosis, and treatment of viral respiratory infections: From influenza virus to SARS-CoV-2 variants. Journal of Nanobiotechnology, **21**, 199 (2023). https://doi.org/10.1186/s12951-023-01938-8

[109] Hussain H., Ganesh A., Milane L., Amiji M.: Lessons learned from the SARS-CoV-2 pandemic; From nucleic acid nanomedicines, to clinical trials, herd immunity, and the vaccination divide. Expert Opinion on Drug Delivery, **20**, 489–506 (2023). https://doi.org/10.1080/17425247.2023.2189697

[110] Kehagia E., Papakyriakopoulou P., Valsami G.: Advances in intranasal vaccine delivery: A promising non-invasive route of immunization. Vaccine, **41**, 3589–3603 (2023). https://doi.org/10.1016/j.vaccine.2023.05.011

[111] Šedová P., Buffa R., Kočí T., Kovářová L., Bednařík J., Vágnerová H., Velebný V.: The effect of aminooxy-linkers' structure on the mechanical properties of hyaluronan-oxime hydrogels. Express Polymer Letters, **16**, 265–278 (2022). https://doi.org/10.3144/expresspolymlett.2022.21

[112] Chapa-Villarreal F. A., Miller M., Rodriguez-Cruz J. J., Pérez-Carlos D., Peppas N. A.: Self-assembled block copolymer biomaterials for oral delivery of protein therapeutics. Biomaterials, **300**, 122191 (2023). https://doi.org/10.1016/j.biomaterials.2023.122191

[113] Knipe J. M., Chen F., Peppas N. A.: Enzymatic biodegradation of hydrogels for protein delivery targeted to the small intestine. Biomacromolecules, **16**, 962–972 (2015). https://doi.org/10.1021/bm501871a

[114] Mei X., Li J., Wang Z., Zhu D., Huang K., Hu S., Popowski K. D., Cheng K.: An inhaled bioadhesive hydrogel to shield non-human primates from SARS-CoV-2 infection. Nature Materials, **22**, 903–912 (2023). https://doi.org/10.1038/s41563-023-01475-7

[115] Ahmed T. A., Eldaly B., Eldosuky S., Elkhenany H., El-Derby A. M., Elshazly M. F., El-Badri N.: The interplay of cells, polymers, and vascularization in three-dimensional lung models and their applications in COVID-19 research and therapy. Stem Cell Research and Therapy, **14**, 114 (2023). https://doi.org/10.1186/s13287-023-03341-4

[116] Zhang J., Yang W., Huang F., Zhang K.: Effectiveness of mRNA and viral-vector vaccines in epidemic period led by different SARS-CoV-2 variants: A systematic review and meta-analysis. Journal of Medical Virology, **95**, e28623 (2023). https://doi.org/10.1002/jmv.28623

[117] Sandoval C., Guerrero D., Muñoz J., Godoy K., Souza-Mello V., Farías J.: Effectiveness of mRNA, protein subunit vaccine and viral vectors vaccines against SARS-CoV-2 in people over 18 years old: A systematic review. Expert Review of Vaccines, **22**, 35–53 (2023). https://doi.org/10.1080/14760584.2023.2156861

[118] Hasanpourghadi M., Novikov M., Ambrose R., Chekaoui A., Newman D., Ding J., Giles-Davis W., Xiang Z., Zhou X. Y., Liu Q., Swagata K., Ertl H. C. J.: Heterologous chimpanzee adenovirus vector immunizations for SARS-CoV-2 spike and nucleocapsid protect hamsters against COVID-19. Microbes and Infection, **25**, 105082 (2023). https://doi.org/10.1016/j.micinf.2022.105082

[119] Borghi M., Gallinaro A., Pirillo M. F., Canitano A., Michelini Z., de Angelis M. L., Cecchetti S., Tinari A., Falce C., Marotti S., Capocefalo A., Chiantore M. V., Iacobino A., di Virgilio A., van Gils M. J., Sanders R. W., Lo Presti A., Nisini R., Negri D., Cara A.: Different configurations of SARS-CoV-2 spike protein delivered by integrase-defective lentiviral vectors induce persistent functional immune responses, characterized by distinct immunogenicity profiles. Frontiers in Immunology, **14**, 1147953 (2023). https://doi.org/10.3389/fimmu.2023.1147953

[120] Mauas R., Urueña A., Cecchini D., Strada M. L., Arietti S., Cassetti I., Nogueira N. F., Salazar A. S., Rodriguez V. J., Jones D. L., Alcaide M. L.: Adverse events and SARS-CoV-2 antibody responses after immunization with Sputnik V, ChAdOx1-S, and BBIBP-CorV vaccines in people with HIV. AIDS, **37**, 941–946 (2023). https://doi.org/10.1097/QAD.0000000000003483

[121] Zhang Q., Kuang G., Zhang L., Zhu Y.: Nanocarriers for platinum drug delivery. Biomedical Technology, **2**, 77–89 (2023). https://doi.org/10.1016/j.bmt.2022.11.011

[122] Solanki R., Shankar A., Modi U., Patel S.: New insights from nanotechnology in SARS-CoV-2 detection, treatment strategy, and prevention. Materials Today Chemistry, **29**, 101478 (2023). https://doi.org/10.1016/j.mtchem.2023.101478

[123] Jha S. K., Imran M., Jha L. A., Hasan N., Panthi V. K., Paudel K. R., Almalki W. H., Mohammed Y., Kesharwani P.: A comprehensive review on pharmacokinetic studies of vaccines: Impact of delivery route, carrier-and its modulation on immune response. Environmental Research, **236**, 116823 (2023). https://doi.org/10.1016/j.envres.2023.116823

[124] Fan B., Gu J., Deng B., Guo W., Zhang S., Li L., Li B.: Positively charged-amylose-entangled Au-nanoparticles acting as protein carriers and potential adjuvants to SARS-CoV-2 subunit vaccines. ACS Applied Materials and Interfaces, **15**, 29982–29997 (2023). https://doi.org/10.1021/acsami.3c05295

[125] Cox M., Peacock T. P., Harvey W. T., Hughes J., Wright D. W., COG-UK Consortium, Willett B. J., Thomson E., Gupta R. K., Peacock S. J., Robertson D. L., Carabelli A. M.: SARS-CoV-2 variant evasion of monoclonal antibodies based on *in vitro* studies. Nature Reviews Microbiology, **21**, 112–124 (2023). https://doi.org/10.1038/s41579-022-00809-7

[126] He J., Duan Q., Ran C., Fu T., Liu Y., Tan W.: Recent progress of aptamer–drug conjugates in cancer therapy. Acta Pharmaceutica Sinica B, **13**, 1358–1370 (2023). https://doi.org/10.1016/j.apsb.2023.01.017

[127] Alejandra W-P., Irene J-P. M., Antonio G-S. F., Patricia R-G. R., Elizabeth T-A., Aleman-Aguilar J. P., Rebeca G-V.: Production of monoclonal antibodies for therapeutic purposes: A review. International Immunopharmacology, **120**, 110376 (2023). https://doi.org/10.1016/j.intimp.2023.110376

[128] Purisima E. O., Corbeil C. R., Gaudreault F., Wei W., Deprez C., Sulea T.: Solvated interaction energy: From small-molecule to antibody drug design. Frontiers in Molecular Biosciences, **10**, 1210576 (2023). https://doi.org/10.3389/fmolb.2023.1210576

[129] Zhu C., Zhang X., Gan J., Geng D., Bian X., Cheng Y., Tang N.: A pH-sensitive hydrogel based on carboxymethylated konjac glucomannan crosslinked by sodium trimetaphosphate: Synthesis, characterization, swelling behavior and controlled drug release. International Journal of Biological Macromolecules, **232**, 123392 (2023). https://doi.org/10.1016/j.ijbiomac.2023.123392

[130] Ju Y-X., Hu R-Z., Wang P-Y., Shen Y-S., Shuang F-F., Wang J., Song P., Zhao W-G., Yao X-H., Zhang D-Y., Chen T.: Strong silk fibroin/PVA/chitosan hydrogels with high water content inspired by straw rammed earth brick structures. ACS Sustainable Chemistry Engineering, **10**, 13070–13080 (2022). https://doi.org/10.1021/acssuschemeng.2c03255

[131] Yang Q., Wang K., Nie J., Du B., Tang G.: Poly(*N*-vinylpyrrolidinone) microgels: Preparation, biocompatibility, and potential application as drug carriers. Biomacromolecules, **15**, 2285–2293 (2014). https://doi.org/10.1021/bm5004493

[132] Yan S., Wu S., Zhang J., Zhang S., Huang Y., Zhu H., Li Y., Qi B.: Controlled release of curcumin from gelatin hydrogels by the molecular-weight modulation of an oxidized dextran cross-linker. Food Chemistry, **418**, 135966 (2023). https://doi.org/10.1016/j.foodchem.2023.135966

[133] Chen N., Chang B., Shi N., Yan W., Lu F., Liu F.: Cross-linked enzyme aggregates immobilization: Preparation, characterization, and applications. Critical Reviews in Biotechnology, **43**, 369–383 (2023). https://doi.org/10.1080/07388551.2022.2038073

[134] Tani Y., Yonenuma R., Mori H.: Clusterization-triggered emission of poly(vinyl amine)-based ampholytic block and random copolymers. Reactive and Functional Polymers, **184**, 105518 (2023). https://doi.org/10.1016/j.reactfunctpolym.2023.105518

[135] Sun Z., Zhu D., Zhao H., Liu J., He P., Luan X., Hu H., Zhang X., Wei G., Xi Y.: Recent advance in bioactive hydrogels for repairing spinal cord injury: Material design, biofunctional regulation, and applications. Journal of Nanobiotechnology, **21**, 238 (2023). https://doi.org/10.1186/s12951-023-01996-y

[136] Kim H-S., Lee H., Kang S., Kim W. J., Shin S.: Diagnostic performance of respirators for collection and detection of SARS-CoV-2. Scientific Reports, **13**, 13277 (2023). https://doi.org/10.1038/s41598-023-39789-w

[137] Kallem P., Hegab H. M., Alsafar H., Hasan S. W., Banat F.: SARS-CoV-2 detection and inactivation in water and wastewater: Review on analytical methods, limitations and future research recommendations. Emerging Microbes and Infections, **12**, 2222850 (2023). https://doi.org/10.1080/22221751.2023.2222850

[138] Wang X., Zhao D., Li Y., Zhou X., Hui Z., Lei X., Qiu L., Bai Y., Wang C., Xia J., Xuan Y., Jiang P., Wang J.: Collagen hydrogel with multiple antimicrobial mechanisms as anti-bacterial wound dressing. International Journal of Biological Macromolecules, **232**, 123413 (2023). https://doi.org/10.1016/j.ijbiomac.2023.123413

[139] Raghav N., Vashisth C., Mor N., Arya P., Sharma M. R., Kaur R., Bhatti S. P., Kennedy J. F.: Recent advances in cellulose, pectin, carrageenan and alginate-based oral drug delivery systems. International Journal of Biological Macromoleculesecules, **244**, 125357 (2023). https://doi.org/10.1016/j.ijbiomac.2023.125357

[140] Mahfufah U., Sultan N. A. F., Fitri A. M. N., Elim D., Mahfud M. A. S., Wafiah N., Friandini R. A., Chabib L., Aliyah, Permana A. D.: Application of multipolymers system in the development of hydrogel-forming microneedle integrated with polyethylene glycol reservoir for transdermal delivery of albendazole. European Polymer Journal, **183**, 111762 (2023). https://doi.org/10.1016/j.eurpolymj.2022.111762

[141] Wang W., Dai J., Huang Y., Li X., Yang J., Zheng Y., Shi X.: Extracellular matrix mimicking dynamic interpenetrating network hydrogel for skin tissue engineering. Chemical Engineering Journal, **457**, 141362 (2023). https://doi.org/10.1016/j.cej.2023.141362

[142] Veisi H., Varshosaz J., Rostami M., Mirian M.: Thermosensitive TMPO-oxidized lignocellulose/cationic agarose hydrogel loaded with deferasirox nanoparticles for photothermal therapy in melanoma. International Journal of Biological Macromolecules, **238**, 124126 (2023). https://doi.org/10.1016/j.ijbiomac.2023.124126

[143] Liu J., Chai J., Yuan Y., Zhang T., Saini R. K., Yang M., Shang X.: Dextran sulfate facilitates egg white protein to form transparent hydrogel at neutral pH: Structural, functional, and degradation properties. Food Hydrocolloids, **122**, 107094 (2022). https://doi.org/10.1016/j.foodhyd.2021.107094

[144] Tolstova T., Drozdova M., Popyrina T., Matveeva D., Demina T., Akopova T., Andreeva E., Markvicheva E.: Preparation and *in vitro* evaluation of chitosan-g-oligolactide based films and macroporous hydrogels for tissue engineering. Polymers, **15**, 907 (2023). https://doi.org/10.3390/polym15040907

[145] Roudsari F. P., Mehrnia M. R., Honarparvaran A., Kaghazian H.: Facile capture of recombinant human erythropoietin on mesoporous affinity hydrogel matrix functionalized with azoboronate. Applied Biochemistry and Biotechnology, **195**, 3456–3476 (2023). https://doi.org/10.1007/s12010-022-04303-x

[146] Widener A. E., Roberts A., Phelps E. A.: Single *versus* dual microgel species for forming guest-host microporous annealed particle PEG-MAL hydrogel. Journal of Biomedical Materials Research Part A, **111**, 1379–1389 (2023). https://doi.org/10.1002/jbm.a.37540

[147] Mao W., Cai X., Pan R., Tang S., Yang F., Cui Y., Sun J., Shen W.: Light-enhanced transparent hydrogel for uric acid and glucose detection by four different analytical platforms. Analytica Chimica Acta, **1239**, 340717 (2023). https://doi.org/10.1016/j.aca.2022.340717

[148] Far B. F., Isfahani A. A., Nasiriyan E., Pourmolaei A., Mahmoudvand G., Rouzbahani A. K., Amin M. N., Naimi-Jamal M. R.: An updated review on advances in hydrogel-based nanoparticles for liver cancer treatment. Livers, **3**, 161–189 (2023). https://doi.org/10.3390/livers3020012

[149] Wang L., Gang X., Xiao X., Ren Y., Wang J., Niu B., Li W.: Sodium alginate/carboxymethyl chitosan-CuO hydrogel beads as a pH-sensitive carrier for the controlled release of curcumin. European Polymer Journal, **192**, 112069 (2023). https://doi.org/10.1016/j.eurpolymj.2023.112069

[150] Chen M., Cui Y., Wang Y., Chang C.: Triple physically cross-linked hydrogel artificial muscles with high-stroke and high-work capacity. Chemical Engineering Journal, **453**, 139893 (2023). https://doi.org/10.1016/j.cej.2022.139893

[151] Gadziński P., Froelich A., Jadach B., Wojtyłko M., Tatarek A., Białek A., Krysztofiak J., Gackowski M., Otto F., Osmałek T.: Ionotropic gelation and chemical crosslinking as methods for fabrication of modified-release gellan gum-based drug delivery systems. Pharmaceutics, **15**, 108 (2023). https://doi.org/10.3390/pharmaceutics15010108

[152] Žigrayová D., Mikušová V., Mikuš P.: Advances in antiviral delivery systems and chitosan-based polymeric and nanoparticulate antivirals and antiviral carriers. Viruses, **15**, 647 (2023). https://doi.org/10.3390/v15030647

[153] Chung J. T., Lau C. M. L., Chung C. H. Y., Rafiei M., Yao S., Chau Y.: Vaccine delivery by zwitterionic polysaccharide-based hydrogel microparticles showing enhanced immunogenicity and suppressed foreign body responses. Biomaterials Sciences, **11**, 4827–4844 (2023). https://doi.org/10.1039/D2BM01960D

[154] Singh P., Ali S. W., Kale R. D.: Antimicrobial nanomaterials as advanced coatings for self-sanitizing of textile clothing and personal protective equipment. ACS Omeg, **8**, 8159–8171 (2023). https://doi.org/10.1021/acsomega.2c06343

[155] Parichenko A., Choi W., Shin S., Stadtmüller M., Akbar T. F., Werner C., Lee J-S., Ibarlucea B., Cuniberti G.: Hydrogel-coated nanonet-based field-effect transistors for SARS-CoV-2 spike protein detection in high ionic strength samples. Engineering Proceedings, **35**, 11 (2023). https://doi.org/10.3390/IECB2023-14566

[156] Huang X., Xu W., Li M., Zhang P., Zhang Y. S., Ding J., Chen S.: Antiviral biomaterials. Matter, **4**, 1892–1918 (2021). https://doi.org/10.1016/j.matt.2021.03.016

[157] Homaeigohar S., Liu X., Elbahri M.: Antiviral polysaccharide and antiviral peptide delivering nanomaterials for prevention and treatment of SARS-CoV-2 caused COVID-19 and other viral diseases. Journal of Controlled Release, **358**, 476–497 (2023). https://doi.org/10.1016/j.jconrel.2023.05.010

[158] Hammond J., Leister-Tebbe H., Gardner A., Abreu P., Bao W., Wisemandle W., Baniecki M., Hendrick V. M., Damle B., Simón-Campos A., Pypstra R., Rusnak J. M.: Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. New England Journal of Medicine, **386**, 1397–1408 (2022). https://doi.org/10.1056/NEJMoa2118542

[159] Guan X., Yang Y., Du L.: Advances in SARS-CoV-2 receptor-binding domain-based COVID-19 vaccines. Expert Review of Vaccines, **22**, 422–439 (2023). https://doi.org/10.1080/14760584.2023.2211153

[160] Kasse C. M., Yu A. C., Powell A. E., Roth G. A., Liong C. S., Jons C. K., Buahin A., Maikawa C. L., Zhou X., Youssef S., Glanville J. E., Appel E. A.: Subcutaneous delivery of an antibody against SARS-CoV-2 from a supramolecular hydrogel depot. Biomaterials Sciences, **11**, 2065–2079 (2023). https://doi.org/10.1039/D2BM00819J

[161] Mehmood Y., Shahid H., Tahir M. A., Abbas M., Farooq U., Khan Z. M., Yousaf H., Uddin M. N., Kazi M.: Remdesivir nanosuspension for potential nasal drug delivery: Determination of pro-inflammatory interleukin IL-4 mRNA expression and industrial scale-up strategy. Journal of Nanoparticle Research, **25**, 129 (2023). https://doi.org/10.1007/s11051-023-05784-5

[162] Zhang H., Wu S., Chen W., Hu Y., Geng Z., Su J.: Bone/cartilage targeted hydrogel: Strategies and applications. Bioactive Materials, **23**, 156–169 (2023). https://doi.org/10.1016/j.bioactmat.2022.10.028

[163] Dahri M., Beheshtizadeh N., Seyedpour N., Nakhostin-Ansari A., Aghajani F., Seyedpour S., Masjedi M., Farjadian F., Maleki R., Adibkia K.: Biomaterial-based delivery platforms for transdermal immunotherapy. Biomedicine and Pharmacotherapy, **165**, 115048 (2023). https://doi.org/10.1016/j.biopha.2023.115048

[164] Do N. H. N., Pham T. H., Le P. K., Ha A. C.: Thermoresponsive chitosan/β-glycerophosphate hydrogels directly post-loading anti-inflammatory diclofenac sodium. Journal of Sol-Gel Science and Technology, **105**, 451–460 (2023). https://doi.org/10.1007/s10971-022-06020-7

[165] Walvekar P., Kumar P., Choonara Y. E.: Long-acting vaccine delivery systems. Advanced Drug Delivery Reviews, **198**, 114897 (2023). https://doi.org/10.1016/j.addr.2023.114897

[166] Loo C-Y., Lee W-H., Zhou Q. T.: Recent advances in inhaled nanoformulations of vaccines and therapeutics targeting respiratory viral infections. Pharmaceutical Research, **40**, 1015–1036 (2023). https://doi.org/10.1007/s11095-023-03520-1

[167] Ousingsawat J., Centeio R., Cabrita I., Talbi K., Zimmer O., Graf M., Göpferich A., Schreiber R., Kunzelmann K.: Airway delivery of hydrogel-encapsulated niclosamide for the treatment of inflammatory airway disease. International Journal of Molecular Sciences, **23**, 1085 (2022). https://doi.org/10.3390/ijms23031085

[168] Nordin A. H., Husna S. M. N., Ahmad Z., Nordin M. L., Ilyas R. A., Azemi A. K., Ismail N., Siti N. H., Ngadi N., Azami M. S. M., Norpi A. S. M., Reduan M. F. H., Osman A. Y., Pratama D. A. O. A., Nabgan W., Shaari R.: Natural polymeric composites derived from animals, plants, and microbes for vaccine delivery and adjuvant applications: A review. Gels, **9**, 227 (2023). https://doi.org/10.3390/gels9030227

[169] Tavares-Negrete J. A., Das P., Najafikhoshnoo S., Zanganeh S., Esfandyarpour R.: Recent advances in lung-on-a-chip technology for modeling respiratory disease. Bio-Design and Manufacturing, **6**, 563–585 (2023). https://doi.org/10.1007/s42242-023-00241-7

[170] Ivanoska-Dacikj A., Oguz-Gouillart Y., Hossain G., Kaplan M., Sivri Ç., Ros-Lis J. V., Mikucioniene D., Munir M. U., Kizildag N., Unal S., Safarik I., Akgül E., Yildirim N., Dedeloğlu A. Ç., Ünsal Ö. F., Herwig G., Rossi R. M., Wick P., Clement P., Sarac A. S.: Advanced and smart textiles during and after the COVID-19 pandemic: Issues, challenges, and innovations. Healthcare, **11**, 1115 (2023). https://doi.org/10.3390/healthcare11081115

[171] Yang T., Li D., Yan Y., Ettoumi F-E., Wu R. A., Luo Z., Yu H., Lin X.: Ultrafast and absolute quantification of SARS-CoV-2 on food using hydrogel RT-LAMP without pre-lysis. Journal of Hazardous Materials, **442**, 130050 (2023). https://doi.org/10.1016/j.jhazmat.2022.130050

[172] George J. E., Manna R., Roy S., Kumari S., Paul D.: Pump-free and high-throughput generation of monodisperse hydrogel beads by microfluidic step emulsification for dLAMP-on-a-chip. BioRxiv, in press (2023). https://doi.org/10.1101/2023.03.12.532292

[173] Parichenko A., Choi W., Shin S., Schlecht M., Gutierrez R., Akbar T. F., Werner C., Lee J-S., Ibarlucea B., Cuniberti G.: Hydrogel-gated silicon nanotransistors for SARS-CoV-2 antigen detection in physiological ionic strength. Advanced Materials Interfaces, **10**, 2300391 (2023). https://doi.org/10.1002/admi.202300391

[174] d'Amone L., Matzeu G., Quijano-Rubio A., Callahan G. P., Napier B., Baker D., Omenetto F. G.: Reshaping de novo protein switches into bioresponsive materials for biomarker, toxin, and viral detection. Advanced Materials, **35**, 2208556 (2023). https://doi.org/10.1002/adma.202208556

[175] Patil A., Patil P., Pardeshi S., Shrimal P., Rebello N., Mohite P. B., Chatterjee A., Naik J.: Combined microfluidics and drying processes for the continuous production of micro-/nanoparticles for drug delivery: A review. Drying Technology, **41**, 1533–1568 (2023). https://doi.org/10.1080/07373937.2023.2167827