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Review

Polymeric Nanoparticles (PNPs) as drug delivery systems for SARS-CoV-2

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Abstract: Researchers from all over the world have been working tirelessly to combat the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) COVID-19 pandemic since the World Health Organization (WHO) proclaimed it to be a pandemic in 2019. Expanding testing capacities, creating efficient medications, and creating safe and efficient COVID-19 (SARS CoV-2) vaccinations that provide the human body with long-lasting protection are a few tactics that need to be investigated. In clinical studies, drug delivery techniques, including nanoparticles, have been used since the early 1990s. Since then, as technology has advanced and the need for improved medication delivery has increased, the field of nanomedicine has recently seen significant development. PNPs, or polymeric nanoparticles, are solid particles or particulate dispersions that range in size from 10 to 1000 nm, and their ability to efficiently deliver therapeutics to specific targets makes them ideal drug carriers. This review article discusses the many polymeric nanoparticle (PNP) platforms developed to counteract the recent COVID-19 pandemic-related severe acute respiratory syndrome coronavirus (SARS-CoV-2). The primary subjects of this article are the size, shape, cytotoxicity, and release mechanism of each nanoparticle. The two kinds of preparation methods in the synthesis of polymeric nanoparticles have been discussed: the first group uses premade polymers, while the other group depends on the direct polymerization of monomers. A few of the PNPs that have been utilized to combat previous viral outbreaks against SARS-CoV-2 are also covered.

Keywords: SARS CoV-2; COVID-19; polymeric nanoparticle; drug delivery

1. Introduction

Nanotechnology is the study and creation of devices and structures at the nanoscale. Because of their ability to increase drug stability, prolong the therapeutic effect of the drug, decrease metabolism of the drug, and reduce cellular uptake, nanoparticles have been the subject of extensive research in the biomedical and biotechnological fields. This is especially true when it comes to drug delivery systems [1].

The rapid evolution of humanity has led to the development of technology that can help us overcome daily struggles. While some advances may not be essential for survival, others are crucial. One such necessary development is the field of vaccine development and delivery. For many years, humans have faced numerous infectious diseases, some of which have proven to be deadly on a global scale, such as the plague, cholera, and various types of coronaviruses. Throughout history, countless pandemics have been caused by viruses, including the Spanish flu.

(H1N1) in 1918 [2], Ebola in 1976, AIDS (HIV) in 1981, avian flu (H5N1) in 1996, SARS (SARSCoV) in 2002, MERS (MERS-CoV) in 2012, and COVID-19 (SARS-CoV-2) in 2019 [3,4]. These outbreaks have taught us valuable lessons about

the importance of novel technologies for testing, tracing, and developing vaccines to effectively respond to pandemics in the future [5,6].

Respiratory tract infections are a major cause of disease and a significant public health concern globally. Lower respiratory tract infections (LRTI) and pneumonia have been reported to be responsible for over four million deaths each year, which is more than the combined deaths caused by HIV, malaria, and tuberculosis. Respiratory viruses are the cause of more than 80% of these infections [7]. An outbreak of the lung illness coronavirus disease 2019 (COVID-19) began in December 2019 in the Chinese city of Wuhan due to a new coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [8,9]. Fever, severe respiratory disease, pneumonia, and dyspnea are the main signs and symptoms of COVID-19 [10,11]. The morphology of SARS-CoV-2 is shown in **Figure 1**. We must prioritize the development of rapid diagnostic testing, drug repurposing, and biomarkers of disease severity, as well as new platforms for vaccine production [12,13].

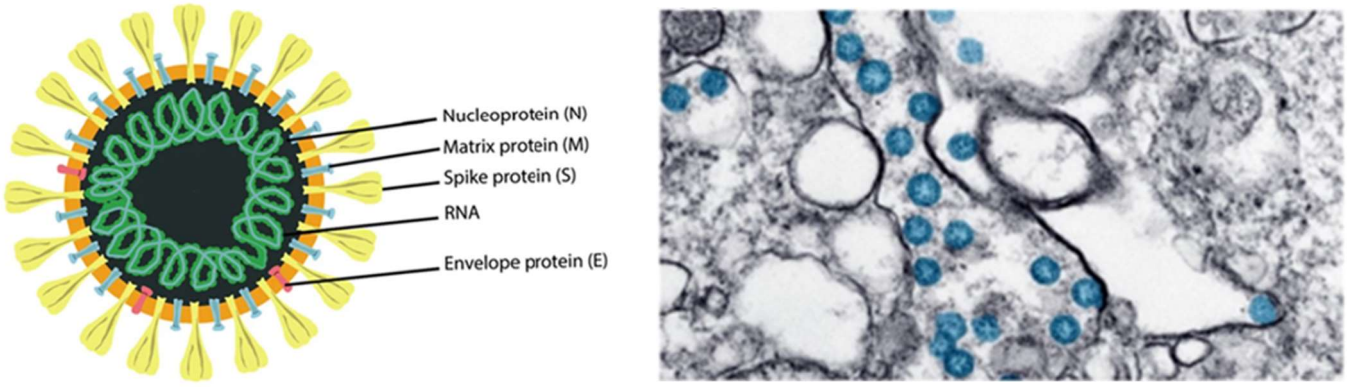

Figure 1. SARS-CoV-2 morphology. **(a)** Representation of the viral structure is illustrated with its structural viral proteins; **(b)** Transmission electron microscope image of SARS-CoV-2 spherical viral particles in a cell. The virus is colorized in blue (adapted from the US Centers for Disease Control) permission from Udugama et al. [22].

One of the most crucial considerations in vaccine development is the availability of platforms that can deliver the vaccine to specific sites in the human body without interfering with other functions [14]. In recent decades, nanoparticles have been developed to address the limitations of free drug molecules and overcome biological barriers at both systemic and cellular levels [15]. This has resulted in the development of new therapeutics to treat a variety of diseases [16]. Various types of nanoparticles are currently in use for different applications [17], but this paper only focuses on Polymeric Nanoparticles (PNPs). PNPs are particles that range in size from 1 to 1000 nm [18] and can be loaded with active compounds that travel through our body to deliver the active compound to the targeted location [19]. PNPs can be divided into two categories: natural and synthetic. Both offer excellent medicinal applicability due to their non-toxicity and biodegradability [20]. PNPs can be modified to control drug release based on receptor proteins, temperature, and pH [21].

This review article discusses various PNPs platforms that have been developed to fight against the most recent pandemic, SARS-CoV-2. The article focuses on the polymeric material, size, design, cytotoxicity, and release mechanism of each NP. It

also covers some of the NPs that have been used against other viral outbreaks but exhibit potential for use against SARS-CoV-2. Common polymers covered in this paper include poly (lactic-co-glycolic acid) (PLGA), poly (ethyleneglycol) (PEG), poly(N-isopropylacrylamide) (PNIPAM), and poly (3,4-ethylene dioxythiophene) (PEDOT).

2. Polymer Nanoparticles (PNPs)

The term "polymeric nanoparticle" refers to solid nanospheres or nanocapsules that either adsorb molecules on their surface or encapsulate them within a polymeric matrix, as shown in **Figure 2** [19,23,24]. Biodegradable polymeric nanoparticles are the most promising drug delivery strategy for pulmonary/respiratory applications [25,26]. PNPs can be used instead of liposomes. They have similar size and shape properties as liposomes but offer additional benefits such as improved stability in vitro and in vivo, high cargo capacity, and targeting. Their ability to efficiently deliver therapeutics to specific targets makes them ideal drug carriers [27]. A wide range of products and application fields, such as electronics, photonics, paints, adhesives, food technology, cosmetics, catalysis, analytical assays, sensors, purifications, and drug administration, have shown interest in polymer particles [28].

Various polymeric structures have been developed for vaccine delivery systems, including solid polymeric nanoparticles, micelles, nanogels, polymersomes, and core-shell nanoparticles [29]. Biocompatible and biodegradable lipids that remain solid at room temperature and body temperature make up solid lipid nanoparticles (SLNs), which are submicron-sized drug carriers [30]. For controlled and targeted delivery, solid lipid nanoparticles (SLNs) are becoming a more viable option than colloidal systems as carriers and amalgamate the benefits of various colloidal carriers, such as emulsions and liposomes, which are physiologically acceptable and can be expected to release drugs from the lipid matrix in a controlled manner, much like polymeric nanoparticles [31,32]. In recent years, the polymeric micelles (PM) system has garnered increasing scientific attention as an effective drug carrier due to its unique properties such as solubilization, selective targeting, inhibition of P-glycoprotein, altered drug internalization route, and subcellular localization [33,34]. Delivering drugs to their targets with micellar solutions of amphiphiles is an efficient method. Owing to the hydrophobic environment present in the core of micelles, drugs that are insoluble in water can be readily dissolved and subsequently transported to the desired locations [35]. Additionally, polymer chains that are cross-linked form three-dimensional networks known as nanogels [36,37]. To improve a wide range of therapies and diagnostic tests for various human diseases, nanogels are widely acknowledged as highly versatile drug delivery systems. Significant volumes of water or biological fluid can be absorbed by these hydrophilic cross-linked polymers that are three-dimensional [38]. A class of artificial vesicles called polymersomes (Ps) is created from synthetic amphiphilic block copolymers. Typical Ps are hollow spheres with a bi-layer membrane enclosing an aqueous solution within [39]. Additionally, Ps have many advantages over liposomes in the delivery of drugs because of their high levels of stability, control over their architecture, adaptability to surface modifications, and high drug loading efficiencies [40]. Understanding how core/shell particles form

has been the subject of several studies, and creating core/shell particles as a practical way to encapsulate a wide range of materials, from organic molecules to biological macromolecules, has drawn a lot of attention [41]. Because bare nanoparticles are toxic, host tissues may be harmed or troubled. Core-shell nanoparticles exhibit better characteristics than bare nanoparticles, including reduced cytotoxicity, high dispersible nature biocompatibility, improved conjugation with drugs and biomolecules because of improved surface properties, and improved chemical and thermal stability [42,43].

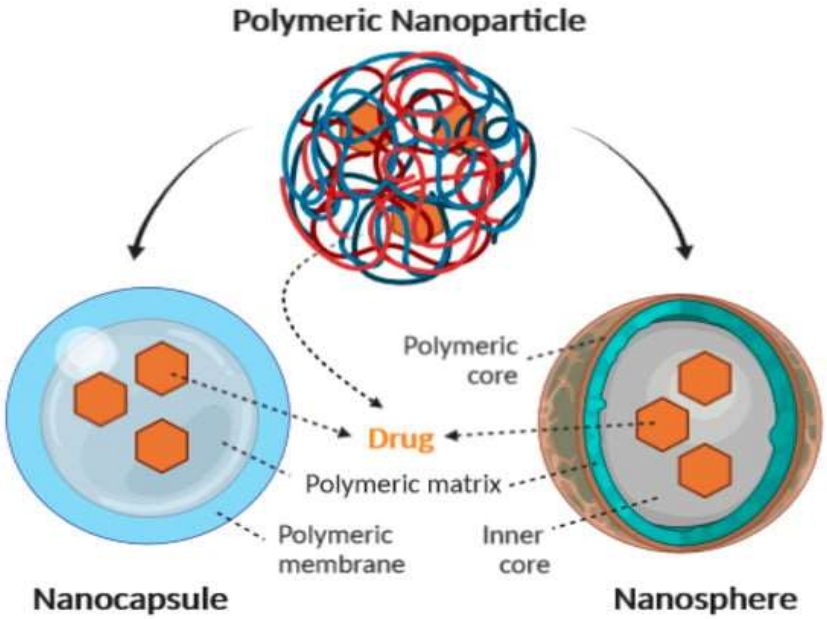

Figure 2. Schematic representation of the structure of nanocapsules and nanospheres. The arrow indicates the presence of drug or bioactive within the nanoparticles. Reproduced with permission from Zielińska et al. [19].

2.1. Synthesis of PNPs

PNPs are created using biodegradable polymers such as polyesters (such as poly(lactideco-glycolide) (PLGA) and poly-caprolactone (PCL), polyamides (such as gelatin and albumin), polyanhydrides, polyurethanes, and polyphosphazenes. These polymers are utilized to produce PNPs [2,44].

Several preparation techniques have been developed; these can be categorized into two groups: those that rely on the polymerization of monomers and those that utilize preformed polymers. These techniques can be further divided into two groups: one-step procedures where the formation of nanoparticles does not require emulsification and two-step procedures that involve the preparation of an emulsification system followed by the formation of nanoparticles in the second step of the process [20].

2.1.1. Emulsification/solvent diffusion (ESD)

This is an altered form of the solvent evaporation technique [45]. To maintain the initial thermodynamic equilibrium of both liquids, the encapsulating polymer is dissolved in a solvent that is partially soluble in water, such as propylene carbonate, and then saturated with water. When the organic solvent is partially miscible with

water, it is necessary to dilute it with excess water to promote the diffusion of the solvent of the dispersed phase; in the opposite case, it is necessary to dilute it with another organic solvent to produce the precipitation of the polymer and the subsequent formation of nanoparticles. The solvent phase that is saturated with polymer and water is then emulsified in an aqueous solution that contains a stabilizer. This process causes the solvent to diffuse to the exterior phase and, depending on the oil-to-polymer ratio, forms nanospheres or nano capsules. Ultimately, the solvent is removed through either filtering or evaporation based on its boiling point. **Figure 3** illustrates the process. Various emulsion types can be employed, but oil/water emulsions are noteworthy due to their use of water as a nonsolvent. This reduces the need for recycling, facilitates the washing step, and minimizes agglomeration, all of which simplifies and enhances process economics [46].

Numerous benefits come with this method, including high encapsulation efficiency (usually >70%), simplicity, ease of scale-up, high batch-to-batch consistency, and narrow size distribution. It also doesn't require homogenization. The large amounts of water that must be removed from the suspension and the water-soluble medication that leaks into the saturated-aqueous exterior phase during emulsification, decreasing the effectiveness of encapsulation, are drawbacks [1,46]. Like a few others, this method works well for encasing lipophilic medications. The ESD method produced several drug-loaded nanoparticles, including meso-tetra (3-hydroxyphenyl) porphine (mTHPP)-loaded PLGA nanoparticles, polylactic acid (PLA) nanoparticles [47,48] loaded with plasmid deoxyribonucleic acid (DNA) [49], PLGA nanoparticles loaded with doxorubicin, PLA nanoparticles loaded with coumarin [46], indocyanine, cyclosporine (CyA)-laden gelatin, and sodium glycolate nanoparticles loaded with cyclosporin (Cy-A) [46,50].

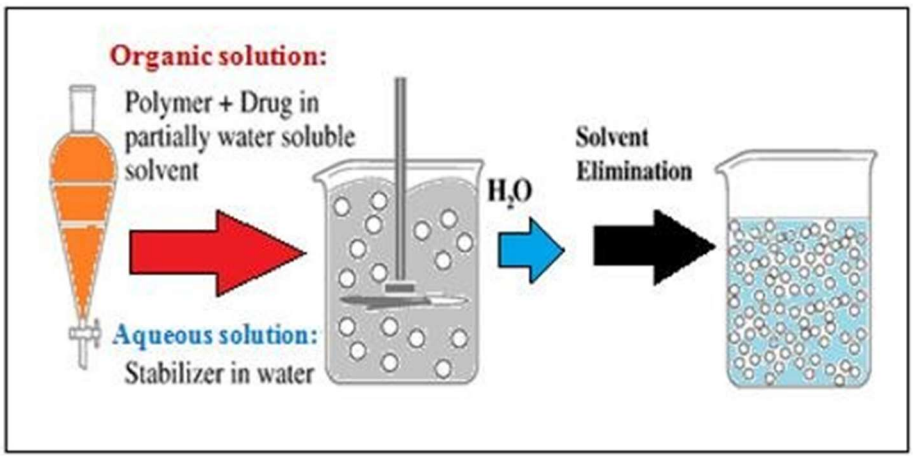

Figure 3. Schematic representation of the emulsification/solvent diffusion technique. Reproduced with permission from Nagavarma et al. [50].

2.1.2. Polymerization of monomers

The previously mentioned technique did not require any polymerization operations; instead, PNPs were produced from premade polymers. During the polymerization of monomers, appropriate polymer nanoparticles can be developed to achieve the required qualities for a certain application. The article discusses methods

for producing PNPs by polymerizing monomers, with a primary focus on three main techniques: mini-, micro-, and emulsion polymerization [51]. Emulsion polymerization remains the most widely utilized and well-proven technique as of 2013. When an aqueous and an organic phase are mixed, spontaneous emulsification takes place in the production of nano-emulsions. Whereas the organic phase is a homogenous mixture of lipophilic surfactant, oil, and water-miscible solvent, the aqueous phase is composed of hydrophilic surfactant and water [52]. PNPs with very small droplets (50–100 nm) will form at the end of the reaction [53]. It is well known that this process raises costs and complicates purification since it needs a lot of surfactants or co-surfactants to create tiny NPs [54]. Thus, Nakabayashi and colleagues [55] used 'acoustic emulsification,' one of the effective methods for producing emulsions quickly and sustainably, to produce poly(methyl methacrylate) (PMMA) NPs with regulated size as shown in **Figure 4**. By employing consecutive ultrasonic irradiation, they created a new synthesis technique for size-controlled PNPs in surfactant-free environments [52]. In **Figure 4**, the original MMA solution in an aqueous solution mixture is shown (a) after 20 kHz for 8 min; (c) 20 kHz for 8 min → 500 kHz; (d) 20 kHz for 8 min → 500 kHz, 10 min → 1.6 MHz, 10 min; and (e) 20 kHz for 8 min → 500 kHz, 10 min → 1.6 MHz, 10 min → 2.4 MHz, 10 min.

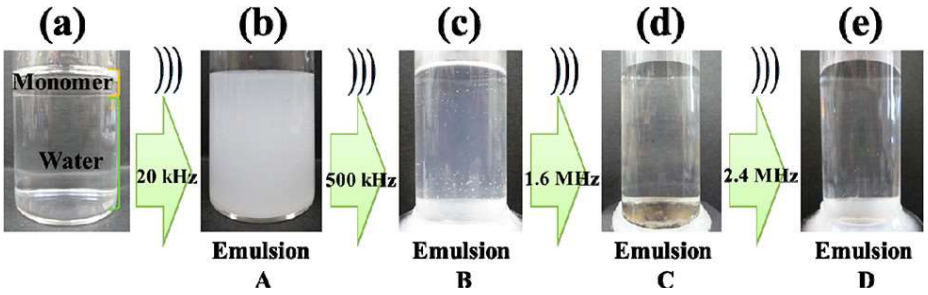

Figure 4. Photographic documentation of MMA in aqueous solution using tandem acoustic emulsification. Reproduced with permission from Nakabayashi et al. [55].

2.2. Characteristics of PNPs

In the fields of nanotechnology and nanomedicine, a wide range of nanomaterials are utilized to deliver drugs with various beneficial properties such as enhanced solubility, extended formulation action, different degrees of lipophilicity or hydrophilicity, and reduced toxicity. Nanoparticle drug delivery systems possess unique physicochemical characteristics including surface properties, shape, size (**Figure 5a**), treatment efficacy, drug release, and loading, among others. The surface properties of nanoparticles can significantly impact the biocompatibility, biodistribution, and pharmacokinetics of the drug molecules [26,56].

2.2.1. Infrared spectroscopy

Fourier transformed infrared spectroscopy (FTIR) is a spectroscopic technique based on the measurement of vibrational transitions between different excitation states of molecules [57]. Tulbah and Lee employed FTIR analysis to investigate potential peak shifts or modifications in the favipiravir solid lipid nanoparticles (FPV-SLN) formulation resulting from the usage of chemicals like Tween 80 and Compritol 888 in the nanoparticle manufacturing process. The FTIR of unprocessed favipiravir

(FPV), measured between 400 and 4000 cm^{-1}, is shown in **Figure 5c**. The C=O, C–F, and C–OH stretching were characterized by stretching peaks at 1659.17, 1259.51, and 1178.64 cm^{-1}, respectively [58].

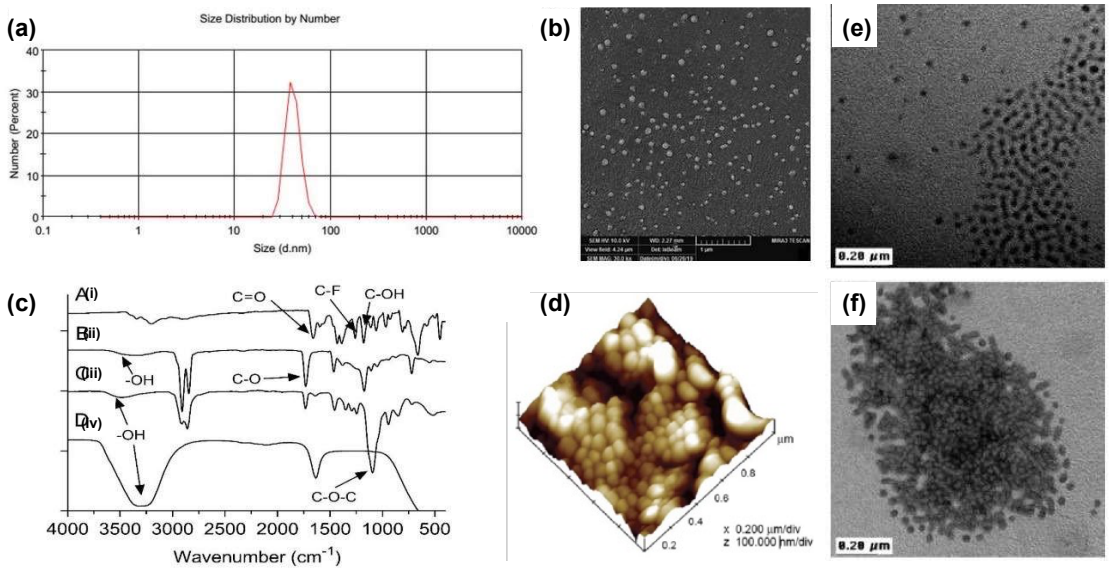

Figure 5. (a–b) Characterization of PLGA-PEG-PLGA NPs loaded with 5FU@Chrysin; **(c)** FTIR spectra of (i) Unprocessed (FPV); (ii) Compritol 888; (iii) Tween 80; and (iv) FPV-SLNs; **(d)** AFM analysis of PEG-g-PLA PNPs' surface morphology; **(e–f)** TEM photographs of bare and hydrogenated spherical PS/PBD core-shell NPs, respectively. Reproduced with permission from Mostafavi et al. [13], Khaledi et al. [59], Tulbah and Lee [58], and Wang et al. [60], respectively.

2.2.2. Scanning electron microscopy

Before being placed on a sample holder and coated with a conductive metal, such as gold, using a sputter coater, the nanoparticle solution needs to be dried out for SEM characterization. After that, a finely focused electron beam is utilized to scan the sample. The secondary electrons that are released from the sample surface provide information about their surface properties. The polymer may be harmed by the electron beam, and the nanoparticles need to be able to endure a vacuum. The SEM mean size and the dynamic light scattering mean size are similar [53]. **Figure 5a,b** shows the particle size distribution and SEM of the size and shape of PLGA-PEG-PLGA loaded with 5FU@Chrysin.

2.2.3. Atomic force microscopy

Atomic force microscopy (AFM) is an additional sophisticated microscopic method for characterizing nanoparticles. This is a novel method for imaging the particles' natural, unaltered form and surface characteristics. This method achieves a spatial resolution of up to 0.01 nm due to the force operating between the probing tip and the surface. It is not necessary for the samples to be conductive, and sample preparation is straightforward. As a result, it permits the examination of samples that are solvent- and hydrate-containing compounds [31,53]. It is used to calculate the force that exists between the sample's particle surface and the probing tip. The technique offers good resolution, easy sample preparation, and quick picture capture. AFM does not require a vacuum, nor does it require a conducting sample [30]. AFM

analysis of PEG-g-PLA PNPs' surface morphology with X-axis scale of 0.200 μm/div is shown in **Figure 5d**.

2.2.4. Transmission Electron Microscope (TEM)

Nanostructures are small, making it impossible to measure their physical properties with conventional methods, which makes them challenging to examine experimentally. Imaging, diffraction, and spectroscopic data of the specimen can be obtained using transmission electron microscopy techniques with an atomic or sub-nanometer spatial resolution, either concurrently or individually [61]. A microscopy method called TEM involves "transmitting" an electron beam through an extremely thin material. The electrons' interaction effects with the sample produce a picture with a resolution of up to 0.08 nm [62]. **Figure 5e**,**f** show TEM of PS/PBD core-shell and hydrogenated PS/PBD nanoparticles.

3. PNPs for Antiviral Drug Delivery Systems

Across the world, there are thousands of committed drug delivery scientists who are working tirelessly to develop vaccines that are safer and more effective against the new variants of SARS-CoV-2. They are also focused on creating new carriers and drug delivery strategies to fight against any future viral pathogens that may emerge [63].

A well-designed delivery system can significantly improve the bioavailability of viral antigens by enhancing cellular uptake, providing metabolic stability, and targeting relevant tissues [64]. The efficacy of antiviral drugs can be enhanced using polymeric nanoparticles that facilitate prolonged drug release and target the virus. Ivermectin, a SARS-CoV-2 inhibitor, has been successfully administered utilizing PLGA-b-PEG-Mal polymeric nanoparticles [16].

One of the main elements influencing drug release is the molecular weight of the polymer. The polymer's chain length can be determined by its molecular weight, where a higher molecular weight corresponds to a longer chain [65]. In addition, the hydrophilicity/lipophilicity of the polymer is reflected in the chain length. Longer chains have a higher lipophilicity and a slower rate of polymer breakdown. Therefore, the drug release kinetics and polymer breakdown rate can be adjusted by adjusting the molecular weight [65,66].

Physical stability, cellular absorption, biodistribution, and drug release are all strongly impacted by particle size, making it a crucial parameter. Nanoparticle performance often improves with decreasing particle size [65]. Some of the effects of nanoparticle grain size are:

- Decrease drug resistance [66].
- Enhance the rate of dissolution [67].
- Increase surface area [68].
- Enhance solubility [69]
- Enhance oral bioavailability [70].
- Decrease toxicity [71].
- Increase the stability of the drug and formulation [68].
- Increase drug-targeting ability [69].

3.1. PLGA

PLGA is a popular polymer used in the creation of micelles, which are used as drug delivery systems. One of the reasons for its widespread use is its high level of biocompatibility and biodegradability. The FDA approved its clinical use in 1989 [72].

In a recent study, researchers aimed to develop a biodegradable drug delivery system that targets specific receptor-binding sites for controlled drug release. They used the commonly used PNP, PLGA, and loaded it with oseltamivir phosphate (OP), a well-known antiviral drug [73]. The PLGA nanoparticles were modified to bind specifically to spike binding peptide-1 (SBP1) of SARS-CoV-2. The size of the OP-loaded NPs and the OP-loaded NPs targeted with SBP1 peptide were reported as 162.0 ± 11.0 and 226.9 ± 21.4 nm, respectively. The drug release study was conducted at a pH of 7.4 and a temperature of 37 °C, and it showed a long and effective release of OP. The release rate was fast for the first 30 days and then steady at about 72 days. There was no burst release of OP, indicating a successful development of the drug delivery system as indicated in **Figure 6** [74].

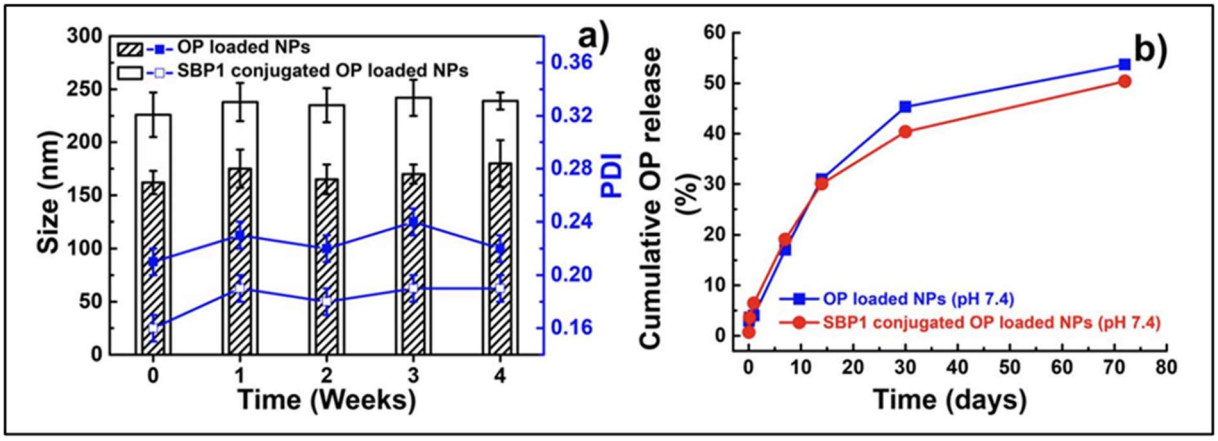

Figure 6. In-vitro stability evaluation and release profile of OP-loaded NPs. **(a)** Size stored at 5 °C for four weeks. **(b)** Release profile of the OP from the NPs targeted with SBP1 peptide or not. Reproduced with permission from Ucar et al. [74]

In another study, PLGA was utilized to administer Fingolimod (FTY720). The NPs were fabricated through a single emulsion solvent evaporation technique, resulting in a positively charged system with reported sizes of approximately 400 and 190 nm for empty NPs and FTY720-NP, respectively. The system demonstrated a notable drug entrapment rate of 90%, with drug release being contingent upon pH [75]. The study found that drug release required an acidic environment, which the developed NPs can access through caveolin-mediated endocytosis and micropinocytosis pathways. Once inside lysosomes, the required acidic environment becomes available to the NPs. The drug release rate at pH 5 was 10%, 80%, and 100% after 2, 8, and 24 h, respectively. However, at pH 7.4, a lower drug release rate of 10%, 10%, and 20% was observed for the same time spans as shown in **Figure 7**. The size of the system remained relatively unchanged over 90 days, and the use of NPs allowed for 70 times higher inhibition of viral infection compared to free drugs. Cytotoxicity studies on human and VeroCCL81 cell lines at 24, 48, and 72 h intervals showed that the

FTY720-NP system was less toxic than the free drug. Overall, the drug delivery system has great potential as it helps preserve the drug until it reaches a specific pH [59].

Similar works were done by Lui and colleagues in 2024 [3], and Struzek and Scherließ in 2023 reported on the preparation of ovalbumin (OVA)-loaded PLGA NP with a size of 700 nm for pulmonary delivery of antigens. They were successfully produced using several principles of quality by design [76]. Also in the work of Chandan and coworkers in 2010, porous PLA and PLGA nanoparticles were tested for pulmonary delivery of the hepatitis B vaccine [77]. Similar work was also done by Claudia and colleagues on the topic "Characterization of polymeric nanoparticles for intravenous delivery: Focus on stability" [78].

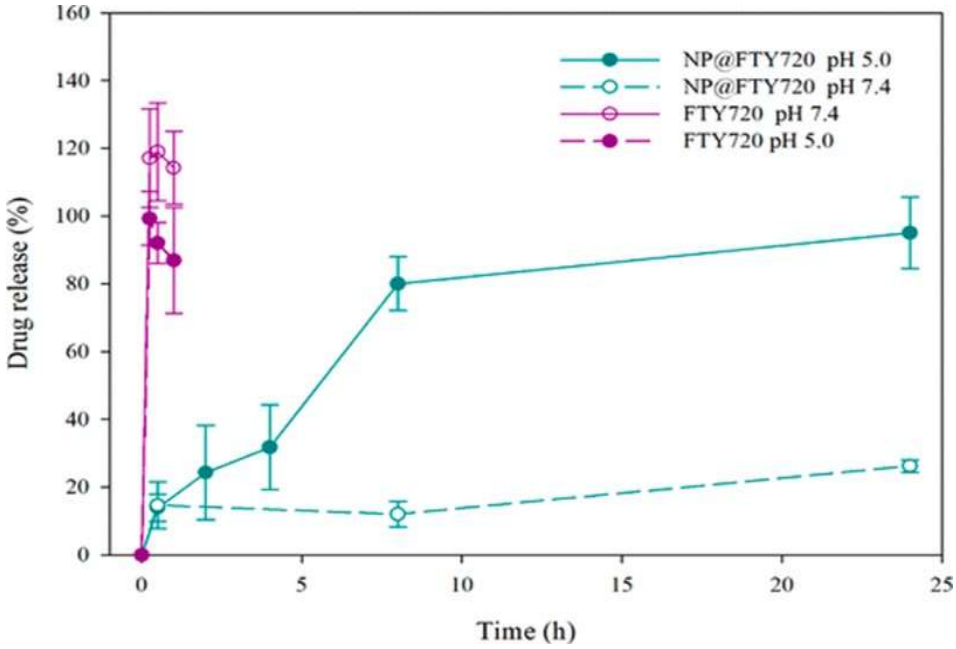

Figure 7. FTY720 release from the nanostructure system. FTY720 release profile from NP@FTY720 in a phosphate buffer with pH 7.4 and an acetate medium with pH 5.0. Data show the average of three independent measurements (n = 3) ± standard deviation (SD). Obtained from Mirinda et al. [75].

3.2. Poly (N-isopropyl acrylamide) (PNIPAM)

Xu and his colleagues developed a drug delivery system that releases drugs in response to specific temperatures. They loaded the FPV drug into silica nanocapsules (SNCs) and functionalized the NCs with block polymers [79,80]. The poly (N-isopropyl acrylamide)-block-poly (N, N-dimethylamino ethyl methacrylate) (PNIPAM-b-PDMAEMA)-modified SNCs were embedded in multilayer films to extend release time. The system can release as low as 50% of the drug over 80 days at 37 and 40 ℃. A morphological stability study showed that the system was unharmed for 80 days, promising an effective drug release for a longer period as indicated in **Figure 8** [79]. **Figure 8c** shows the schematic representation of "on-demand" temperature-triggered film swelling and drug release from multilayer films.

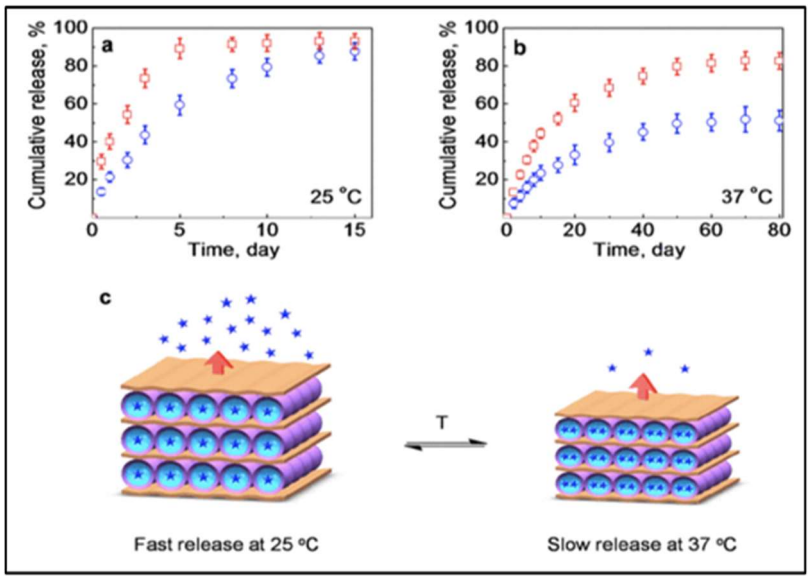

Figure 8. Release kinetics of FPV from [SNC-g-PNIPAM-b-PDMAEMA/PMAA]3 (squares) and [SNC-g-PNIPAM-b-Q100M/PMAA]3 (circles) films at **(a)** 25 and **(b)** 37 °C; **(c)** Schematic representation of mechanism. Reproduced with permission from Xu et al. [79].

In a study also conducted by Xu and colleagues, they coated silica nanocapsules (SNCs) with block polymers and loaded Molnupiravir into the system [81]. Molnupiravir is a drug that was approved for the treatment of SARS-CoV-2 from its early days. The block copolymer was quaternized to a certain degree to control the steric hindrance around the charged groups of the polymer blocks in the capsule. The entire SNC-Block polymer nanoparticle system was then embedded in well-defined films with polystyrene sulfonate (PSS) homopolymers by layer-by-layer self-assembly via electrostatic interaction. The polymer that the study group coated on SNCs was PNIPAM-bPDMAEMA, which is sensitive to temperature change. Therefore, the drug release was dependent on the temperature [81]. Speaking of how Molnupiravir operates, it introduces copying errors during viral RNA replication. The average thickness of various combinations of the system, namely [SNC-g-PNIPAM-b-PDMAEMA/PSS], [SNC-g-PNIPAM-b-Q20M/PSS], [SNC-g-PNIPAM-bQ40M/PSS], and [SNC-g-PNIPAM-b-Q100M/PSS] films, were reported as 125 ± 16, 135 ± 19, 170 ± 25, and 205 ± 28 nm, respectively, at 37 °C. The drug release was found to be around 81, 76, 62, and 45 % from [SNC-g-PNIPAM-b-PDMAEMA/PSS]3, [SNC-g-PNIPAM-b-Q20M/PSS]3, [SNC-g-PNIPAM-b-Q40M/PSS]3, and [SNC-g-PNIPAM-b-Q100M/PSS]3 films after 80 days, respectively [81] as shown in **Figure 9**. Like the previous study, the drug release was found to be faster as the temperature was decreased, and the reason behind this could be the temperature-induced hydration of PNIPAM moieties in LBL films, as per the researchers [81]. The transition of the delivery system in terms of its thickness was found to be reversible even after going through so many temperature-manipulating cycles, suggesting the system to be robust [81]. The overall design of this drug delivery system, where steric hindrance in the amino group of QPDMAEMA moieties was enhanced and the quaternization degree, the thickness of the film layer, and molecular diffusion distance were increased, allowed a reduction in the drug release from the nanoparticle system [81].

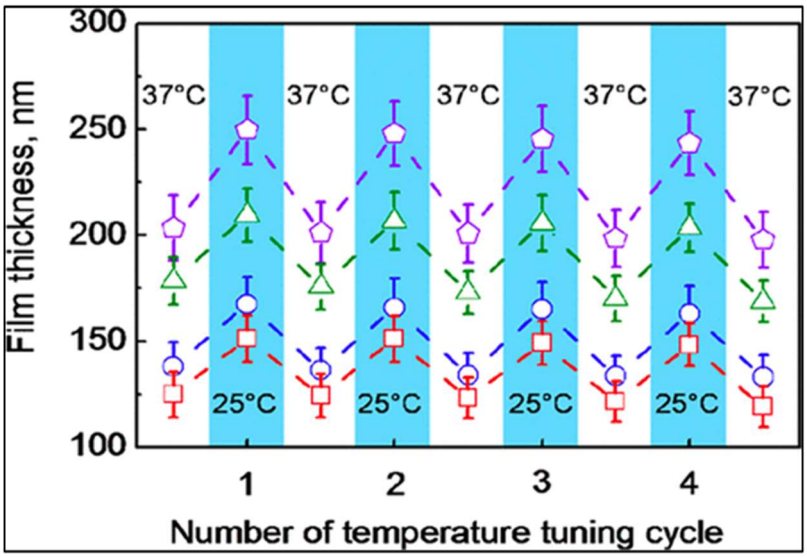

Figure 9. Reversible temperature-triggered swelling/deswelling of [SNC-g-PNIPAM-b-PDMAEMA/PSS]3 (squares), [SNC-g-PNIPAM-b-Q20M/PSS]3 (circles), [SNC-g-PNIPAM-bQ40M/PSS]3 (triangles), and [SNC-g-PNIPAM-b-Q100M/PSS]3 (pentagons) films at 25 and 37 ℃, respectively. Reproduced with permission from Xu et al. [81].

3.3. PEG/PLGA-b PEG

Moving on, the next system was developed using PLGA-b-PEG-Mal nanoparticles in which the Ivermectin drug (IVM) was loaded, and this can be delivered orally [82]. The reported size of nanoparticles was 70-80 nm with a 20% feed capability of IVM [82]. The goal of the researchers was to develop a system that can decrease the expression of viral spike protein present on SARS-CoV-2 as well as down-regulate its receptor protein (ACE2), and therefore they attached an Fc immunoglobulin fragment forming T-Fc-IVM-NPs (IgG Fc antibody-treated IVM-NPs) [82]. The mechanism of action of this NP system has been reported by the researchers in the paper, but for now, it is important to know that the results of western blotting showed a significantly lower spike protein and ACE2 in the HEK293T and HELA cells when T-Fc-IVM-NPs were administered, but not by free IVM [82]. The cytotoxic results reported suggest that the free IVM decreases basal and maximum [82] respiration and severely impacts ATP production inside the mitochondria of cells; however, no such side effects were observed when NT-IVM-NP (not treated IVM-NPs) and T-Fc-IVM-NP were administered to the cells [82]. This result shows a great possibility of decreasing the spread of any virus from the SARS family, including SARS-CoV-2, as the system targets the spike proteins present on the surface of each member of this family [82].

Up next, we found another study that used Ivermectin (IVM), which was loaded in synthetic nanoparticles: Poly (L-lactide-co-glycolide)-block-poly (ethylene glycol)-amide (PLGA-b-PEG-NH2); PLGA-b-PEG-Mal.; Poly (L-lactide-co-glycolide)-block-poly (ethylene glycol)-hydroxide (PLGA-b-PEG-OH), against Zika virus [16,83]. The goal of this group was to develop a platform that allows the delivery of IVM at a higher concentration without affecting other cellular functions inside our body. They created a system whose size was found to be 60 nm at IVM fed of 10%

and 140 nm at IVM fed of 50%; however, they also reported the NP system was only stable up to 30% fed [82]. They reported that the targeted T-Fc-IVM-NPs were successfully able to cross the intestinal epithelial barrier model and enter the bloodstream in comparison to non-targeted NT-OH-IVM-MPs. Specifically, 65% of injected targeted NP was distributed in the blood after 24 h, and the rest (24%) was still in different parts of the intestine [83]. A comparison study with free IVM showed that most of the drug was stuck in intestinal tissue, indicating that the NPs are needed to cross that intestinal barrier [83]. The study also reported that the free IVM was easily able to cross the placental membrane in comparison to that of T-Fc-IVM-NPs; however, the free IVM completely disrupts the cellular respirations of the cell that forms the placental barrier, but this is not the case for T-Fc-IVM-NPs [83]. The overall cytotoxic study showed that the toxicity of IVM is significantly reduced when loaded with polymeric NPs, as indicated in **Figures 10** and **11** [83]. Specifically, **Figures 10 A,B** show the western blot decreasing expression of ACE2 in A549 adenocarcinoma alveolar basal epithelial cells transfected with a plasmid expressing spike protein with the treatment of IVM, NT-IVM-NPs, or T-Fc-IVM-, while **Figure 10C** shows the ACE2 expression in HeLa malignant epithelial cells. Immunofluorescence staining in **Figure 10D** confirms the same trend in A549 cells. Additionally, the researchers also reported that T-FC-IVM-NP can reduce NS1 protein, suggesting its usage could be beneficial against the ZIKA virus and other viral infections [83]. Taking their word as it is, one can tweak this NP system to target the spike proteins present in SARS-CoV-2.

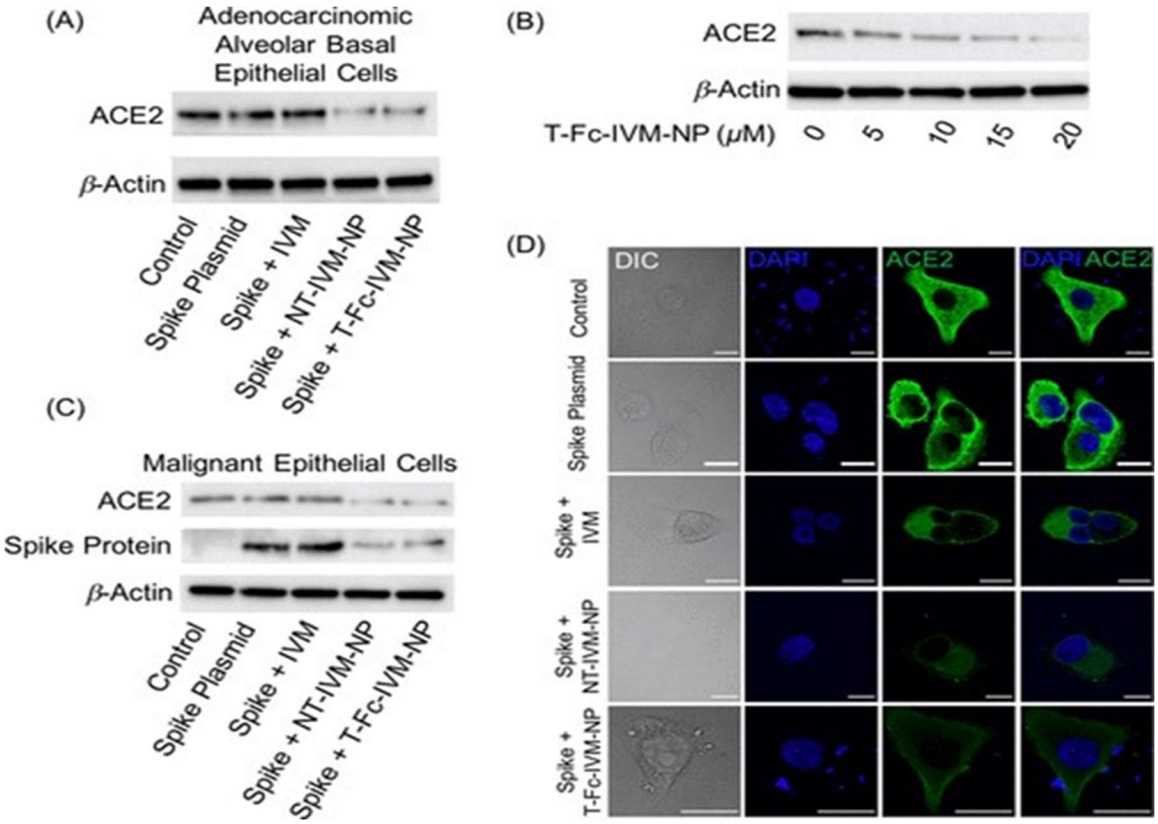

Figure 10. Expression of ACE2 with the treatment of IVM, NT-IVM-NPs, or T-Fc-IVM-NPs. Reproduced with permission from Surnar et al. [83].

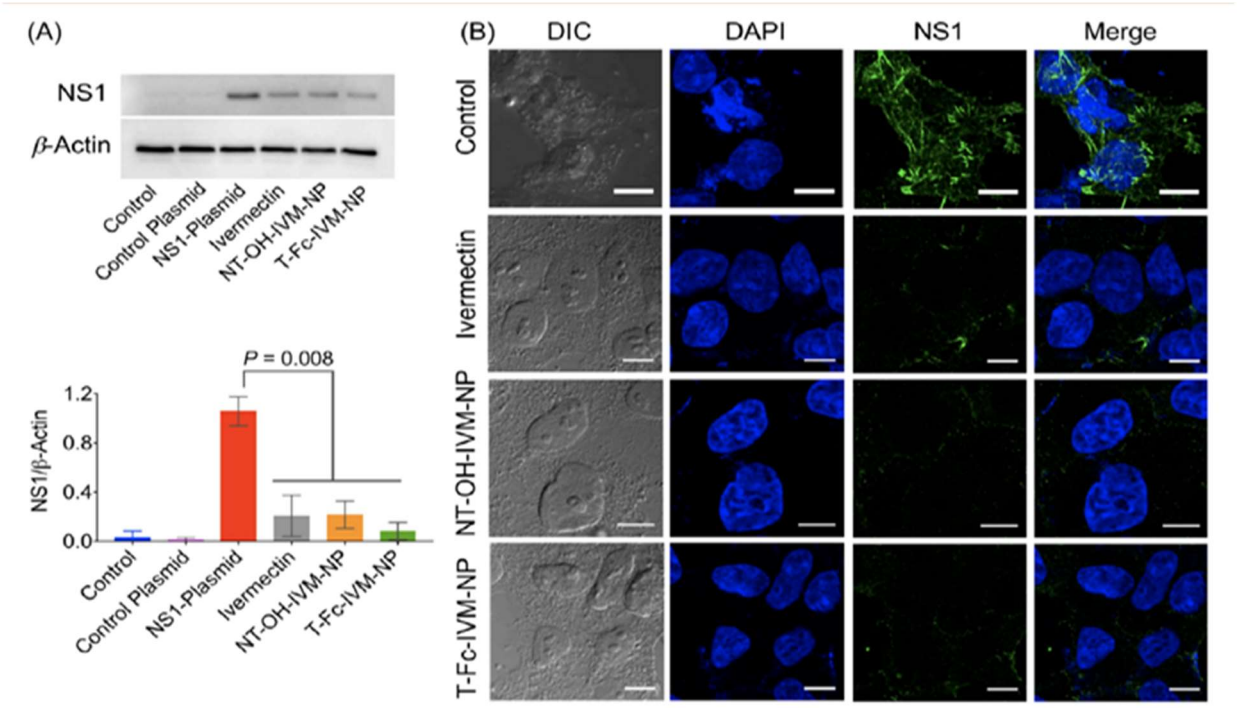

Figure 11. NS1 expression level in HEK293T cells after treatment with NPs by (A) Western blotting and (B) immunofluorescence. Cells were treated with IVM, NT-OH-IVM-NP, or T-Fc-IVM-NP at a concentration of 10 μM concerning IVM for 6 h—scale bar: 10 μM. Reproduced with permission from Surnar et al. [83].

3.4. PEDOT

We found a new study that used a unique system that responds to electricity. The researchers used curcumin (CUR), an antiviral and anticancer drug, and combined it with electrospun poly(ε-caprolactone) (PCL) microfibers (MFs) loaded with poly (3,4-ethylene dioxythiophene) nanoparticles (PEDOT NPs). The PEDOT NPs, which are polymeric nanoparticles, have a diameter of 99 ± 21 nm and are located inside the PCL MFs [84]. The study reported that when external stimuli were applied after embedding PEDOT NPs in the electro-fiber, the release of CUR was promoted [84]. Although the release of CUR by simple diffusion was very low, a linear increase in drug release was observed with the increased number of potential pulses. Notably, this increase in the release was not observed when PEDOT was excluded from the system, indicating that their presence is crucial for responding to electrical stimuli in the form of potential pulses in a PBS + Tween 20 electrolyte medium, mimicking a physiological environment. The study found that the specific increases with the number of pulses for PCL/PEDOT/CUR MFs were 8.1% ± 4.3%, 18.4% ± 7.2%, and 30.2% ± 10.2% after 1, 3, and 5 potential pulses, respectively [84]. The increase is based on the voltametric response of PEDOT NPs, which results in volume variations and structural changes [84]. The drug system's cytotoxic study revealed that cell growth decreases only when PEDOT is not used, indicating that the presence of PEDOT also reduces the toxicity of CUR, as shown in **Figure 12** [84]. In conclusion, this study shows the potential for using PCL/PEDOT/CUR MFs to control drug release in response to electrical stimulation within our bodies, regardless of the virus we are dealing with.

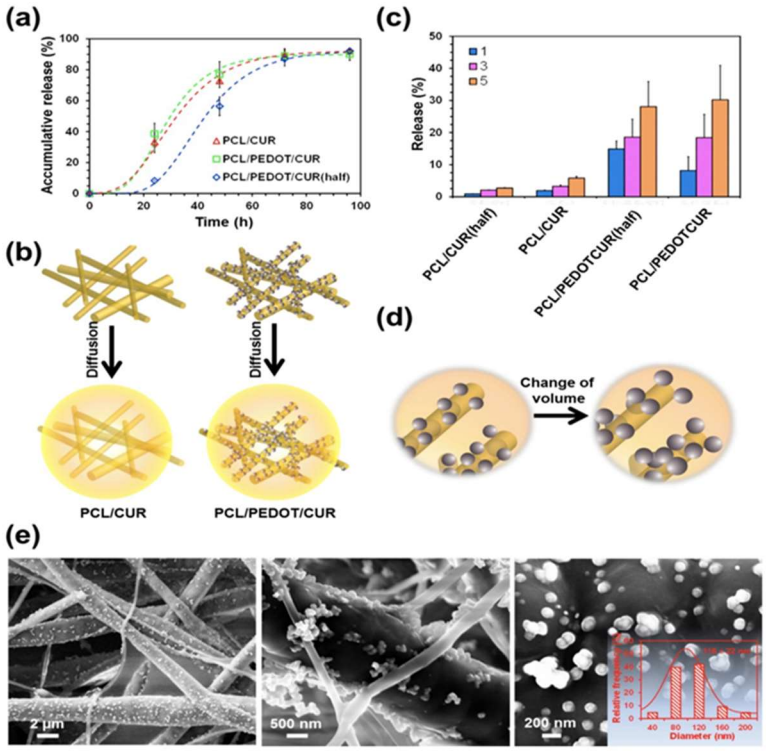

Figure 12. CUR release from PCL/CUR and PCL/PEDOT/CUR MFs. **(a,c)** CUR release profiles in PBS-EtOH, and after electrostimulation by applying 1, 3, and 5 consecutive potential pulses, respectively; **(b,d)** Scheme representing the diffusion mechanism for CUR release in the absence/presence of electrostimulation, respectively; **(e)** SEM micrographs of PCL/PEDOT/CUR fibers after electrostimulation. Reproduced with permission from Puiggali-Jou et al. [84].

4. Conclusion

According to the findings, the utilization of PNPs presents numerous therapeutic benefits in combating the SARS-CoV-2 virus. PNPs provide a means of effectively delivering drugs to targeted locations for a prolonged period, thereby saving considerable costs associated with repeated drug administration due to quick elimination from the body. **Table 1** shows a list of selected PNPs used for anti-viral drug delivery strategies.

Table 1. List of selected PNPs used for anti-viral drug delivery strategies.

Polymer	Conjugate	Properties	Application	Ref
PLGA	PLGA-b-PEG-NH_2 OVA-PLGA	water-insoluble, biocompatibility, and biodegradability	drug delivery of hydrophilic as well as hydrophobic actives, diabetic retinopathy, neovascular age-related macular degeneration (ocular neovascularization)	[76], [85–87]
PEDOT	PCL/PEDOT/CUR	electrical conductivity, electrochemical activity, thermoelectric behavior, and high specific capacitance.	facilitating cell spreading and enhancing cell proliferation	[84], [88–90]
PNIPAM	PNIPAM-b-PDMAEMA	temperature-triggered hydration−dehydration transition, high surface areas, and irregular structures	temperature-modulated drug delivery systems	[81], [91], [92]
PEG	T-Fc-IVM	biocompatibility, protein repellent ability,	immunodeficiency disease, bioconjugation, and drug delivery	[93], [94]

Table 1. (*Continued*).

Polymer	Conjugate	Properties	Application	Ref
Remdesivir	Remdesivir-GS-5734	the heterocyclic part analogous to adenine, allowing hydrogen bonding, contains C-nucleoside, the presence of a 1′-CN group, the ribosyl moiety ensuing inhibition of RNA (instead of DNA) synthesis, and the presence of a phosphoramidate group, contributing to its tissue targeting	Activity against Ebolavirus, Filo-, Pneumo and Paramyxoviruses	[95]
PCL	PEO-PCL	excellent biocompatibility, high hydrophobicity, and neutral biodegradation end products	used as emulsifying agents, solubilizing agents, surfactants, wetting agents, and treating HIV/AIDS	[96]
PVA	PVA-TPU-Ag	antibacterial and antiviral properties	wound dressings, medical device coatings, treatment of COVID-19	[97]
PLA	PLA-Ag	high mechanical strength, biocompatibility and non-toxicity	biomedical packaging, food packaging, and 3D printing technology.	[98]
PNIIPAM	PNIPAM	high stability, biocompatibility,	Treat HIV-1 infection	[99]

Additionally, various studies have shown that PNPs significantly reduce the cytotoxicity of many drugs on vital cells within the body. Given their biodegradability, PNPs are promising contenders for replacing current drug delivery systems with polymeric nanoparticle-based systems for COVID-19. Some PEG-based nanoparticle systems have already been applied in clinical trials for COVID-related treatment [100]. Additionally, PEG-PLGA systems have been widely applied in clinical trials for anti-cancer treatment [101,102] and hence one can expect these platforms to be approved for coronavirus-related trials as well in the near future. The number of nanoparticles in clinical approvals has gone up each year since 1992 and saw a total of 32 approvals in 2020, a part of which were for COVID-19 vaccines [103]. Further, the number of human clinical trials peaked in 2021 for various nanoparticle systems, which only provides a bright prospect for the upcoming future.

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Abbreviations

AFM	atomic force microscopy
CUR	Curcumin
Cy-A	cyclosporin
DNA	deoxyribonucleic acid
ESD	emulsification/solvent diffusion
FTIR	Fourier transformed infrared spectroscopy
FPV	Favipiravir
FPV-SLN	favipiravir solid lipid nanoparticles
FTY720	Fingolimod
H_1N_1	Spanish flu, lower respiratory tract infections

IVM	Ivermectin drug
Mal	Maleimide
MFs	Microfibers
mTHPP	meso-tetra (3-hydroxyphenyl) porphine
NH_2	Amide
OP	oseltamivir phosphate
OVA	Ovalbumin
PBD	Polybutadiene
PCL	poly-caprolactone
PBS	polybutylene succinate
PEDOT	Poly (3,4-ethylene dioxythiophene)
PLA	polylactic acid
PLGA	Poly (lactic-co-glycolic acid)
PM	polymeric micelles
PMMA	Poly (methyl methacrylate)
PNIPAM-b-PDMAEMA	Poly (N-isopropyl acrylamide)-block-poly (N, N-dimethylamino ethyl methacrylate)
PNIPAM	Poly (N-isopropyl acrylamide)
PEG	Poly (ethylene glycol)
PNP	polymeric nanoparticle
PS	Polystyrene
Ps	Polymersomes
PSS	polystyrene sulfonate
SARS-CoV-2 COVID 19	Severe Acute Respiratory Syndrome Coronavirus 2
SBP1	spike binding peptide
SEM	scanning electron microscopy
SD	standard deviation
SLNs	solid lipid nanoparticles
SNCs	silica nanocapsules
TEM	transmission electron microscope
WHO	World Health Organization

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