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Review

Trends in the development of remdesivir based inventions against COVID-19 and other disorders: A patent review

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A B S T R A C T

The development of remdesivir has been a breakthrough for COVID-19 treatment. It has been approved in about 50 countries, including Saudi Arabia, since 2020. The generic structure of remdesivir was first disclosed in 2005. This patent review summarizes the remdesivir based inventions to treat/prevent COVID-19 and other disorders from 2009 to May 16, 2021, emphasizing the patents related to medical and pharmaceutical sciences. The primary patents/patent applications of remdesivir are related to its compositions, new combinations with other therapeutic agents, delivery systems, and new indications. The inventive combinations have displayed synergistic effects against COVID-19, whereas the delivery systems/compositions have improved patient compliance. The inventions related to new indications of remdesivir to treat Ebola, hepatitis, idiopathic pulmonary fibrosis, diabetic nephropathy, and cardiovascular complications enhance its therapeutic area. Many new innovative combinations and delivery systems of remdesivir are anticipated to provide better treatment for COVID-19.

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**Introduction**

COVID-19, a communicable pandemic infection, was first noticed in Wuhan, China, in December 2019. It is triggered by a new single-stranded virus (SARS-CoV-2). The general signs of COVID-19 comprise fatigue, fever, cough, loss of smell/taste, and shortness of breath. Some people may develop ARDS (acute respiratory distress syndrome) due to cytokine release, septic shock, and blood clots. Accordingly, it may be fatal in some patients [1]. By May 16, 2021, about 162,177,376 confirmed cases of COVID-19 had been reported globally, approximately 3,364,178 people have died of COVID-19, and 1,264,164,553 people have been vaccinated [2]. The World Health Organization (WHO) has issued guidelines, advice, and situation reports regularly to the general public and health workers about COVID-19 [3]. Many reviews have discussed the epidemiology, diagnosis, treatment, vaccines, and challenges of dealing with COVID-19 [4–9].

**Remdesivir (GS-5734)**

Remdesivir (Fig. 1) is a tetrahydrofuran based pyrrolo-triazine derivative (MF: C_{27}H_{35}N_{6}O_{8}P; MW: 602.6; CAS Number: 1809249-37-3), which has been developed by Gilead Sciences [7]. In May 2020, the United States Food and Drug Administration (USFDA) approved an Emergency Use Authorization (EUA) to remdesivir [10], wherein the USFDA fully approved it on October 22, 2020. Remdesivir is indicated to treat COVID-19, which is subjected to certain conditions (Table 1). First, it must be administered in a healthcare center or hospital, providing acute care similar to inpatient hospital care because remdesivir intravenous (IV) infusion must be administered by a trained professional. Second, remdesivir is approved for COVID-19 patients >12 years of age and weighing >40 kg because of the established safety and efficacy clinical studied. The recommended dosage of remdesivir in COVID-19 patients comprises a single loading IV infusion of remdesivir (200 mg) on day 1 followed by a maintenance dose (100 mg) from day 2 via IV infusion (30–120 min). The recommended treatment duration is not less than 5 days and not more than 10 days. The USFDA has also allowed the EUA to remdesivir to pediatric COVID-19 patients of <12 years of age and weighing between 3.5 to 40 kg because of the severity of COVID-19, higher benefit to risk ratio, and lack of adequate or suitable alternative of remdesivir [11]. As of May 16, 2021, remdesivir has been approved in about 50 countries since 2020 to treat COVID-19. These countries include Australia, India, United Arab Emirates, Argentina, Japan, Canada, Lebanon, Russia, Great Britain, European Union (about 30 countries), United States of America, Brazil, Israel, Guatemala, Qatar, Iraq, Saudi Arabia, South Korea, Kuwait, Hong Kong, Turkey, Switzerland, Singapore, Bahrain, Mexico, Jordan, and Taiwan [12].

**Pharmacology of remdesivir**

The SARS-CoV-2 mainly affects the respiratory tract and the enterocytes of the gastrointestinal tract. It requires RNA-dependent RNA polymerase (RdRp) to replicate [13–16] (Scheme 1).

Remdesivir, a phosphoramidite prodrug, enters the cell and breaks into its monophosphate form. This monophosphate form

![Fig. 1. Remdesivir (GS-5734).](image-url)

| Table 1 |
|---|
| The Rx data of remdesivir. |
| **Active ingredient (Proprietary name; Applicant name; NDA number)** | **Dosage form (Route; Strength)** | **Approval date (Marketing status)** | **Indication** | **Exclusivity (Expiry date)** |
| Remdesivir (Veklury; Gilead Sciences; N214787) | Powder (Intravenous; 100 mg/vial) | October 22, 2020 (Prescription) | Treatment of COVID-19 in adults and pediatric patients (at least 12 years of age and 40 kg) requiring hospitalization | New chemical entity (October 22, 2025) |
| solution (Intravenous; 5 mg/ml) |
converts to remdesivir triphosphate (RDV-TP, GS-443902, Fig. 2) after phosphorylation. The RDV-TP incorporates into the RdRp complex in place of ATP and inhibits its activity [11,14]. Remdesivir shows poor affinity towards RNA polymerase II and mitochondrial RNA polymerase. Accordingly, it is supposed to possess a good safety profile in humans [8]. The single-dose (3–225 mg) clinical studies of remdesivir have demonstrated its non-toxic and tolerable effects [8]. Remdesivir is absorbed fast, has a moderate duration of action with an elimination half-life of about one hour, shows protein binding of about 88–93%, and about 74% is excreted via urine [11,17]. The significant metabolites of remdesivir are GS-704277 (Fig. 3), GS-441524-MP (Fig. 4), and GS-441524 (Fig. 5) [10,17,18] (Scheme 2).

Nausea is the most common side effect of remdesivir. Remdesivir can cause allergic reactions during its infusion or after the infusion. Consequently, the remdesivir treatment must be discontinued in patients showing clinically significant hypersensitivity to remdesivir or any component of its product. The remdesivir dose (150 mg) for 7–14 days revealed a reversible increase in the liver enzymes, for example, alanine aminotransferase and aspartate transaminase [8]. Besides, remdesivir can also lead to an increase in the prothrombin time [11]. Therefore, liver function tests and determination of the prothrombin time are recommended before and during the remdesivir therapy. The injection of remdesivir is prepared in sulfobutylether-β-cyclodextrin (SBED), which can cause renal dysfunction due to its accumulation in the kidney. Consequently, patients exhibiting an eGFR of <30 ml/min are not recommended to take remdesivir [8,11]. Accordingly, the testing of the eGFR has to be done before the start of remdesivir therapy [8–11]. As of date, there is no data on the overdose and antidote of remdesivir. The overdose cases must be monitored and handled based on the sign, symptoms, and clinical status of the patient [11]. No published report establishes reproductive, teratogenic, developmental toxicity of remdesivir [8].

Clinical trials on remdesivir

Many combinations of remdesivir with other drugs, for example, lopinavir, ritonavir, interferon beta-1a & 1b, merimepoddib, NA-831, baricitinib, dexamethasone, tocilizumab, risankizumab, lenzilumab, plitidepsin, and hydroxochloroquine, are in a clinical trial to treat COVID-19 [19]. However, it is also in a clinical trial for other conditions [20], which is provided in Table 2.

Some critical patent reviews on coronavirus have been published [21–25]. These articles mention the name of remdesivir but are silent about its patent literature. The authors believe no review discusses remdesivir based patent inventions/innovations to treat...
COVID-19. This review updates the scientific fraternity about the existing inventions/innovations of remdesivir. It will help them generate innovative ideas to provide better remdesivir based treatments for COVID-19.

**Methodology**

**Patent literature searching**

The updated patent searching (June 14, 2021) was performed through Espacenet, WIPO, USPTO, and Scifinder databases. The exact structure search of remdesivir and its CAS number search was done by the Scifinder database. The keywords remdesivir and GS-5734 were used for patent search in the Espacenet, WIPO, and USPTO databases (Scheme 3). The compound patents of remdesivir were identified using the exact structure search of remdesivir in the Scifinder database.

**Exclusion criteria**

The patents/patent applications that do not use the terms “remdesivir or GS-5734” or the chemical structure of remdesivir specifically or generically in the claim section of the patent/patent application were excluded from the final list. The patents/patent applications related to the novel synthetic compounds as antiviral agents have not been included in this review because these compounds have never been tested in humans. The data of cited patents/applications in this review are provide in Table 3.

**Translation of non-English patents/patent applications**

The translation of the non-English patents/patent applications was obtained from Espacenet and WIPO databases.

**Results**

**Compound patents of remdesivir**

**US10065958B2** provides ribosides, riboside phosphates, and produgs for treating infections caused by the Paramyxoviridae virus family, particularly for respiratory infections of syncytial parainfluenza virus. This patent covers remdesivir and its salts. The patent exemplifies the respiratory syncytial virus antiviral activity of the disclosed compounds and their cytotoxicity assays [26].

**US8008264B2** claims the general structure of remdesivir. It also claims a method of treating a viral infection (dengue, yellow fever, etc.) using the disclosed compounds alone or in a combination of other therapeutic agents [27]. **US8318682B2** [28] and **USRE46762E** [29] also claim the general structure of remdesivir to treat viral diseases. These three patents exemplify the antiviral activity of the disclosed compounds, including the IC$_{50}$ and EC$_{50}$ values of the Hepatitis C virus.

**US9724360B2** [30] and **US9944994B2** [31] unveil ribosides, riboside phosphates, produgs thereof, and their pharmaceutical compositions to treat Ebola, Cueva, and Marburg viral infections. These patents specifically cover the specific isomer of remdesivir (Fig. 1) to prepare its marketed dosage forms. They also exemplify
the anti-Ebola virus activity and the cytotoxicity assays of the stated compounds.

**Polymorph patents of remdesivir**

**US10836787B2** claims the crystalline form of remdesivir. The disclosed crystalline form is claimed to have a bioavailability advantage, physical stability and is suitable to manufacture the solid dosage forms for the intended therapeutic use. The patent also mentions the method of preparation of the claimed polymorph [32].

**Pharmaceutical compositions of remdesivir to treat/prevent COVID-19**

**Pharmaceutical composition of remdesivir for monotherapy**

**US10695361B2** claims a method of treating Coronaviridae infection (SARS, MERS, 229E, NL63, OC43, and HKU1) by administering a pharmaceutical composition (solid dosage forms, injectable, and emulsion, etc.) of remdesivir. This is the primary patent that covers the use of remdesivir to treat SARS-CoV-2 infection. The patent exemplifies the activity of the compounds against SARS-CoV in Mice and MERS-CoV in rhesus monkeys [33].

**US10675296B2** relates to a lyophilized composition containing remdesivir (1%–10%) and cyclodextrin, for example, sulfobutylether-β-cyclodextrin sodium (90%–99%), for treating infections caused by Arenaviridae, Coronaviridae, Filoviridae, Flaviviridae, or Paramyxoviridae family viruses. The claimed composition showed enhanced solubility and improved usability for parenteral administration. The claimed composition may optionally contain a pH adjusting agent like sodium hydroxide or hydrochloric acid. The composition of remdesivir with β-cyclodextrin can deliver varying required doses of remdesivir without precipitation of remdesivir and are compatible with other IV solvents. This patent covers the marketed dosage form of remdesivir to treat COVID-19. The patent exemplifies the preparation of lyophillized/injectable composition and its stability testing [34].

**US20200360292A1** discloses an anhydrous composition (e.g. liquid, or capsule) comprising an oil-soluble hydrophobic drug (e.g. remdesivir), an oil-soluble hydrophobic surfactant (e.g. dodecyl maltoside), and a pharmaceutically acceptable carrier (e.g. Miglyol.RTM. 812, and Vitamin E), wherein the drug and the surfactant are dissolved in the pharmaceutically acceptable carrier. This oral formulation is claimed to possess enhanced bioavailability of the hydrophobic drug from the gastrointestinal tract. Since remdesivir is a hydrophobic drug, such formulation (e.g. soft gel capsules) is ideal for it. This patent exemplifies the preparation of oil-based formulations of cannabinoid, which is also a hydrophobic drug [35].

**WO202010376A1** claims a composition comprising highly porous activated carbon (microporous carbon) and an antiviral

| Condition (Intervention) | NCT number | Phase (Location) | Sponsor/collaborator (Funder type) | Status (Study start) | Study completion (Last update) |
|--------------------------|------------|------------------|-----------------------------------|---------------------|-------------------------------|
| Ebola/HIV/AIDS (Remdesivir) (NCT04385719) | 2 (Uganda) | Makerere University; University of Liverpool, and EDCTP (Other) | The study has not started recruiting participants (July 2020) | June 2021 (May 13, 2020) |
| Pneumonia/viral (Remdesivir) (NCT04728880) | Unknown (Egypt) | Mansoura University (Other) | Recruiting (January 26, 2021) | May 30, 2021 (January 28, 2021) |
| COVID-19 pneumonia (Remdesivir and Tocilizumab) (NCT04409262) | 3 (United States) | Hoffmann-La Roche, and Gilead Sciences (Industry) | Completed (June 16, 2020) | March 8, 2021 (March 11, 2021) |
| Ebola (GS-5734) (NCT02818582) | 2 (Guinea and Liberia) | National Institute of Allergy and Infectious Diseases, and National Institutes of Health Clinical Center (NIH) | Completed (July 1, 2016) | August 31, 2020 (September 30, 2020) |
| Acute respiratory distress syndrome (Remdesivir and hydroxychloroquine) (NCT04321616) | 3 (Norway) | Oslo University Hospital (Other) | Recruiting (March 28, 2020) | November 2020 (April 14, 2020) |
| Ebola virus (Remdesivir, ZMapp, MAb114, and REGN-EB3) (NCT03719586) | 2/3 (United States and The Democratic Republic of the Congo) | National Institute of Allergy and Infectious Diseases, and National Institute of Allergy and Infectious Diseases (NIH) | Completed (November 21, 2018) | August 18, 2020 (December 4, 2020) |

**Table 2**

Clinical trial on remdesivir for new conditions.
| Patent/patent application number^a | Assignee | Expiry date^b | Status^c | Ref. no. |
|-----------------------------------|----------|---------------|----------|---------|
| US10065958B2 | Gilead Sciences | September 16, 2031 (Due to patent term adjustment (PTA) of 230 days) | Patent term extension (PTE) filed at USPTO | [26] |
| US80082648B2 | Gilead Sciences | September 6, 2029 (PTA of 198 days) | PTE filed at USPTO | [27] |
| US8311862B2 | Gilead Sciences | April 22, 2029 | PTE filed at USPTO | [28] |
| USRE46762E | Gilead Sciences | April 22, 2029 | PTE filed at USPTO | [29] |
| US9724360B2 | Gilead Sciences | October 29, 2035 | PTE filed at USPTO | [30] |
| US9949948B2 | Gilead Sciences | October 25, 2035 | PTE filed at USPTO | [31] |
| US10836787B2 | Gilead Sciences | April 27, 2038 | Patented case | [32] |
| US10809361B2 | Gilead Sciences | September 16, 2036 | Patented case | [33] |
| US10576979B2 | Gilead Sciences | July 10, 2038 | Patented case | [34] |
| US2006360292A1 | Aegis Therapeutics | May 15, 2040 | Under examination | [35] |
| WO2020210376A1 | University of Illinois | April 8, 2040 | No national phase entry | [36] |
| CN11190434A9 | The Fourth Military Medical University | April 30, 2040 | Under examination | [37] |
| CN112675143A | Gu Shihai | February 8, 2041 | Publication | [38] |
| CN112402371A | Nanjing Zhengji Medical Research Company Limited | November 19, 2040 | Under examination | [39] |
| CN11265675A | Henan Taifeng Biotechnology Company Limited | January 23, 2041 | Publication | [40] |
| US110302940B1 | Jubilant Generics Limited | July 14, 2040 | Patented case | [41] |
| US10052884B2 | Gholam Peyman | May 12, 2035 | Patented case | [42] |
| WO202022753A1 | Massachusetts Institute of Technology and The General Hospital Corporation | May 7, 2040 | No national phase entry | [43] |
| WO2020202111A1 | Tarsus Pharmaceuticals | April 3, 2040 | No national phase entry | [44] |
| CN111467362A | Beijing Ash Drug Institute Company Limited | May 9, 2040 | Under examination | [45] |
| CN112168956A | Hefei TianTai Technology Company Limited | September 30, 2040 | Under examination | [46] |
| CN111297838A | Ningbo Hekang Biomedical Technology Company Limited | April 8, 2040 | Under examination | [47] |
| CN111149804A | Jiangsu Refontech Industrial Company Limited | February 24, 2040 | Under examination | [48] |
| CN111956630A | Dalian University of Technology | August 20, 2040 | Under examination | [49] |
| CN11251525A | Jiangsu Xinxin Advanced Functional Fiber Innovation Center Company Limited | October 30, 2040 | Under examination | [50] |
| US11013688B1 | Softlens NV | July 16, 2040 | Patented case | [51] |
| CN112801327A | Chen Xijing | March 3, 2041 | Publication | [52] |
| CN111603040A | Huang Zhulin | June 23, 2040 | Under examination | [53] |
| US10251898B2 | Gilead Sciences | October 25, 2035 (Due to terminal disclaimer with US9949948B2) | Patented case | [54] |
| US10695357B2 | Gilead Sciences | October 25, 2035 (Due to terminal disclaimer with US10251898B2) | Patented case | [55] |
| CN112618557A | Beijing Jiajun Technology Company Limited | January 19, 2041 | Publication | [56] |
| CN112494500A | Beijing Jiajun Technology Company Limited | November 26, 2040 | Under examination | [57] |
| CN112274520A | Tianjin Jikun Pharmaceutical Technology Company Limited | November 23, 2040 | Under examination | [58] |
| WO2021067480A1 | University of Washington | September 30, 2040 | No national phase entry | [59] |
| CN112843073A | Institute of Animal Science and Veterinary Medicine | March 30, 2041 | Publication | [60] |
| US20200384034A1 | Spiritus Therapeutics | June 4, 2040 | Under examination | [61] |
| CN112522030A | The Fifth Affiliated Hospital of Sun Yat-Sen University | November 23, 2040 | Under examination | [62] |
| CN11159259A4 | Peking University | March 13, 2040 | Under examination | [62] |
| WO2021038296A2 | Tonix Pharma Holdings Limited | August 27, 2040 | No national phase entry | [64] |
| WO2021010458A1 | Tonix Pharma Holdings Limited | July 1, 2040 | No national phase entry | [65] |
| CN112135625A | Guangzhou Xinchuangy Medicine Clinical Research Company Limited | May 9, 2040 | No national phase entry | [66] |

^a Excluding process-related patents/applications.
^b Based on the twenty years from the date of filing of the patent application. If the patent application is not granted to patent, or patent is lapsed/revoked, then it is available for public use.
^c Status as of May 16, 2021, from USPTO and Espacenet.

It states that charcoal has antiviral effects. The antiviral agents may be adsorbed and encapsulated within microporous carbon, causing a persistent release of the drug that generates a more considerable therapeutic effect. Due to the kidney function-related benefits, this charcoal-based drug delivery system avoids the renal toxicity issues associated with some antiviral agents, e.g. acyclovir. This patent application does not exemplify any formulation of remdesivir [36].

CN11149434A9 covers a fast-dissolving oral form of remdesivir comprising film-forming materials (e.g. methylcellulose and ethyl-
cellulose etc.), surfactants (e.g. Tween 80 and lecithin), plasticizers (e.g. polyethylene glycol and polypropylene glycol), correctives (e.g. xylitol and fructose) and auxiliary materials (e.g. antioxidants and preservatives). The claimed film is fast-acting, easy-to-carry and use, simple to prepare, and patient compliant. The patent application exemplifies the preparation of the fast-dissolving oral film of remdesivir [37].

CN112675143A claims a film-coated tablet of remdesivir comprising a pH regulator (Eudragit L100-55, fumaric acid, sodium citrate, tartaric acid, succinic acid, and sodium hydroxide). The pH regulator of the tablet adjusts the pH to 3.4 ± 0.5 and 7.5 ± 0.5 of the gastric-coated tablet and the enteric-coated tablet, respectively. The claimed tablet showed long-term stability, good bioavailability, and is convenient to use. The patent exemplifies preparation of claimed tablet comprising remdesivir, carboxymethyl cellulose sodium (disintegrant), hydroxypropylmethyl cellulose or polyvinylpyrrolidone (binder), magnesium stearate (lubricant), microcrystalline cellulose (filler), and different pH regulators; disintegration time of tablets in artificial gastric juice and artificial intestinal juice; and stability testing of the tablets [38].

CN112402371A claims remdesivir injection comprising remdesivir (50–200 mg), polysorbate (e.g. polysorbate-20), and absolute ethanol. The injection has a short and straightforward production process. Remdesivir has excellent solubility in the non-viscous and non-aqueous mixture of absolute ethanol and polysorbate. The non-viscous mix is suitable for sterilization and injection preparation. The non-aqueous environment increases the stability of the injection. The injection’s pH, close to neutral, ensures patient safety and compliance. The patent application exemplifies the preparation of remdesivir injection and the quality testing methods [39].

CN112656759A claims remdesivir eye drops (1 mg–200 mg/ml) comprising an osmotic pressure regulator (glycerin, sodium chloride, and potassium chloride), an antioxidant (sodium sulfite and sodium bisulfite), a pH regulator (e.g. boric acid), a bacteriostatic agent (benzalkonium chloride, and benzyl alcohol), and a solvent (water for injection). The claimed eyedrop can be used for treatment, including eyelid virus infection, conjunctival virus infection, corneal virus infection, and retinal virus infection. The patent application exemplifies the preparation of remdesivir eye drops and its stability testing [40].

US101020349B1 claims a sublingual tablet for COVID-19 treatment comprising remdesivir (0.1 mg to about 50 mg), a pH regulator (citric acid), and other excipients, wherein the tablet can release at least 80% of the remdesivir in 15 min or less. The pH regulator helps to prevent the degradation of remdesivir. The claimed tablet offers numerous advantages over other drug delivery systems, including better chemical stability of remdesivir due to the pH regulator, adequate shelf-life, respectable pharmaceutical properties, steady drug release, faster onset of action, lower dosage, enhanced efficacy, and promising safety profile of remdesivir. The patent mentions the formula of preparing the claimed sublingual tablet in its examples. One of the formula comprises remdesivir, mannitol (diluent), HPMC (binder), sodium starch glycolate (disintegrant), sodium alginate (carrier), sodium lauryl sulfate (surfactant), citric acid (pH adjusting/salivating agent), talc (glidant), magnesium stearate (lubricant), butylated hydroxyanisole (preservative), sucralose (sweetener), milk protein concentrate (mucoadhesive), and a solvent (aqueous, alcoholic or acidic) [41].

**Pharmaceutical composition of remdesivir with other drugs**

US10925889B2 claims treatment of a medical condition (COVID-19) by administering one or more antiviral medications (e.g. remdesivir) together with one or more cell pathway inhibitors (i.e. anti-inflammatory agents) dissolved in a non-toxic aerosolized semifluorinated alkane (e.g. F4H5, F4H6, F4H8, F6H6 F6H8, etc.). The semifluorinated alkane evaporates quickly after inhalation and leaves the biocompatible antiviral and anti-inflammatory drugs at the desired location to produce their respective effects. The patent exemplifies a clinical study wherein a COVID-19 patient was treated with an inhaled combination comprising remdesivir, a Wnt inhibitor, and a protease inhibitor dissolved in a semifluorinated alkane for three weeks through which the patient recovered [42].

WO2020227530A1 relates to compositions comprising pyrimidine compound (uracil, uridine, thymine, thymidine, cytosine, and cytidine) and an antimicrobial agent (e.g., remdesivir) to treat an infection (COVID-19). The pyrimidine compound increases the susceptibility of microbe towards antimicrobial agents and potentiates antimicrobial agent efficacy. In one exemplary embodiment, the pyrimidine is administered together with remdesivir by intra-venous infusion. However, the details of these examples are not provided in this patent application [43].

WO2020202111A1 reveals treatment of a viral infection (COVID-19) by administering a pharmaceutical composition comprising an isoxazoline parasiticide (fluralaner, sarolaner, lotilaner, afoxolaner, fluxametamide, and isocycloseram) and an antiviral agent (e.g. remdesivir). The claimed combination is said to have a synergistic effect. However, no experimental details of the combination of isoxazoline parasiticide and remdesivir have been provided in this patent application [44].

CN111467362A claims a pharmaceutical composition comprising azithromycin and remdesivir to treat an infectious disease (COVID-19), wherein the particle size of azithromycin is 40–400 μm, and the D90 particle size is 200–400 μm. The particle size of azithromycin is responsible for its improved absorption. The patent application exemplifies the preparation of azithromycin compositions with different particle sizes and the effect of azithromycin particle size on blood concentration. There is no example wherein azithromycin has been combined with remdesivir [45].

CN112168956A claims an antiviral spray that contains a viral protease inhibitory polypeptide, ethanol extract of Scutellaria serrate, and remdesivir. The spray can inhibit SARS-CoV-2 replication, inhibit inflammation, promote mucosal repair, and achieve the preventive and therapeutic effects of the new coronavirus. The patent application mentions preparing the claimed spray without demonstrating its efficacy against COVID-19 [46].

CN111297838A discloses an antiviral drug inhalation spray comprising active antiviral agent (remdesivir), adjuvant (azithromycin, roxithromycin, clindamycin, and erythromycin), taste-masking agent (xylitol, sorbitol, and mannitol), and a solvent (water, propylene glycol, or glycerol). The claimed spray can deliver the drugs into the respiratory tract to prevent virus infection and its transmission. The combined medication spray produces a synergistic therapeutic effect that reduces the drug dose and the side effects. The patent application provides antiviral drug inhalation spray preparation but does not provide experimental efficacy against COVID-19 [47].

**New delivery systems of remdesivir**

CN111149804A provides a spray comprising antiviral agent (e.g. remdesivir), surfactant (disodium lauryl sulfosuccinate monoester), stabilizer (amino trimethylene phosphate), protective agent (sodium sulfate), and deionized water. The spray is safe, durable, convenient to use, durable, and can inhibit the growth and reproduction of viruses. The patent application provides a process to prepare claimed spray but does not disclose its efficacy data against COVID-19 [48].

CN111956630A offers a liquid preparation (pH = 3.5–5.5) for nebulizers comprising 1–100 mg/ml of remdesivir and a solvent (e.g. sulfobutyl-β-cyclodextrin, ethanol, water, or their mixture). The atomized remdesivir released from the nebulizer acts on the primary site of infection (nasal cavity, oral cavity, and lungs), mak-
ing the medication more effective. This also reduces the systemic exposure of the drug in the body and helps to minimize the side effects of remdesivir. The patent application discloses the preparation method of remdesivir solution liquid preparation for nebulizer, but it is silent about the experimental efficacy of the claimed nebulizer [49].

CN112515258A claims a three-layered mask. The middle layer of the mask is removable and is an anti-viral medical nanofiber mask film material (polyvinyl alcohol, cellulose acetate, and polyvinylidine fluoride) with an antiviral drug (remdesivir). The claimed mask inhibits the proliferation of viruses, including SARS-CoV-2, during use, avoids the virus spread, and protects the individual. The patent application exemplifies the preparation of a three-layered mask [50].

US11013688B1 claims a method for the treatment of a viral infection (COVID-19) by administering 1 µl–50 µl of a medically active liquid comprising remdesivir utilizing a soft-mist-inhaler. The soft-mist-inhaler described in this patent delivers remdesivir with high precision and reproducibility. This patent exemplifies the preparation of remdesivir solutions employing water, ethanol, and ethylene glycol, which were dispensed utilizing a soft-mist-inhaler [51].

CN112891327A provides a liquid preparation for remdesivir atomized inhalation and its preparation. The content of remdesivir in the liquid preparation ranges from 0.1% to 0.5% (w/v), and the pH ranges from 5 to 7. This delivery system increases the exposure of remdesivir in the lungs much higher than that of intravenous injection, which reduces the dosage, cost, and systemic side effects [52].

Cosmetic preparation of remdesivir

CN111603408A claims a lipstick containing remdesivir. The development of such lipstick has positive significance in the ongoing pandemic. The claimed lipstick inhibits SARS-CoV-2 propagation on the exposed parts of the human body, shortens the virus’s survival time, and reduces the risk of infection. It has been demonstrated that the virus loses activity within 30 min after exposure to this lipstick. The examples of preparing remdesivir based lipstick are provided in the patent application [53].

New indications of remdesivir

US10251898B2 claims a method of treating infections caused by the Filoviridae virus, ebola virus, and other related viral conditions by administering a pharmaceutical composition (solid dosage forms, injectable, and emulsion, etc.) of remdesivir. The composition may optionally contain another therapeutic agent (corticosteroid, bronchodilator, anticholinergic, and mucolytic agent). The patent exemplifies the activity of claimed compounds against the Ebola Virus and Nipah-GFP HMVEC-TERT Cells [54].

US10695357B2 claims treatment of Nipah virus infection using a pharmaceutical composition (solid dosage forms, injectable, emulsion, etc.) of remdesivir, alone or in combination with other drugs like ribavirin, favipiravir, and palivizumab. The patent exemplifies the activity of claimed compounds against the Ebola Virus and Nipah-GFP HMVEC-TERT Cells [55].

CN112618557A discloses pharmaceutical composition (powder, tablet, granule, capsule, oral liquid, emulsion, or mixture. Suspension) to treat or prevent cardiovascular complications of diabetes (coronary heart disease, atherosclerosis, hyperlipidemia, high cholesterol). The effective dose of remdesivir is 100 mg–200 mg per day for a 60 kg individual. The composition may optionally comprise an anti-diabetic and cardiovascular agent. Remdesivir displayed a protective effect on kidney function, reduced blood lipids, and the risk of cardiovascular disease in exemplified animal models [56].

CN112494500A discloses the application of remdesivir in the prevention/treatment of cardiotoxicity caused by the anti-tumor drug (anthracyclines, taxanes, fluorouracils, trastuzumab, and bevacizumab). Thus, remdesivir can effectively protect myocardial cells and maintain normal cardiac function. The patent application exemplifies the effects of remdesivir in animal models (doxorubicin-induced mouse injury model) [57].

CN112274520A claims the application of remdesivir and its salts to prepare a medicine for treating idiopathic pulmonary fibrosis. It has been demonstrated that remdesivir can improve forced vital capacity, inhalation, and exhalation airway resistance; reduce lung collagen content and the area of pulmonary fibrosis. The patent application exemplifies the claimed effect of remdesivir on bleomycin’s idiopathic pulmonary fibrosis model [58].

WO2021067480A1 relates to a composition for treating a hepatitis B virus (HBV) infection using a RIG-1 agonist (e.g. N-(6-benzamido-1,3-benzothiazol-2-yl)naphthalene-2-carboxamide), a vehicle for intracellular delivery (e.g. Liposome, nanocapsule, nanoparticle, exosome, microparticle, microsphere, and lipid particle), and a pharmaceutically acceptable carrier. This composition may further include an antiviral agent (e.g. remdesivir). The patent application does not provide any experimental evidence of the claimed treatment with remdesivir [59].

CN112843073A claims the application of remdesivir to treat Bovine parainfluenza virus type 3 (BPIV3). The invention states and exemplifies that remdesivir inhibits/inactivates the BPIV3 virus by blocking its replication without any toxic effect [60].

Miscellaneous

US20200384034A1 covers extracellular vesicles (EVs) recovered from a virus-infected (COVID-19) patient. These EVs can be used in combination with antiviral agents (remdesivir) to attenuate/treat the severity of the infection. No example of remdesivir and EVs combination has been provided in this patent application [61].

CN112522203A provides cell vesicles expressing a chimeric antigen receptor loaded with remdesivir to kill SARS-CoV-2. The cell vesicles can also neutralize SARS-CoV-2 and avoid the production of antibody enhancement effects. The antiviral agent (e.g. remdesivir) can be better delivered to the site, where SARS-CoV-2 gathers, and the side effects of drugs can also be reduced. The patent application exemplifies the preparation of cell vesicles loaded with remdesivir [62].

CN111592594A provides new monoclonal antibodies with high binding activity and neutralizing activity against SARS-CoV-2 to provide effective means for preventing or treating COVID-19. The sequence IDs of the monoclonal bodies are depicted in the description of the patent application. It also claims a pharmaceutical composition comprising remdesivir with the claimed monoclonal antibody. However, no experimental evidence of the combination of remdesivir and the claimed monoclonal antibody has been exemplified in the patent application [63].

WO2021038296A2 claims a method for treating COVID-19 using a composition comprising a TFF2 polypeptide modified by PEGylation or polysialylation. The compositions may also include an agent that inhibits or reduces SARS-CoV-2 replication (remdesivir). The TFF2 protects the gastrointestinal mucosa from injury by stabilizing and bolstering making gels, reducing inflammation, and stimulating epithelial reestablishment. The patent application is silent about the experimental details of the combination of remdesivir with TFF2 polypeptide [64].

WO2021001458A1 provides isolated anti-CD154 antibodies that bind to mammalian CD-154. The CD-154 is involved in cell-mediated immunity, and its activation boosts immunity. This patent application claims an isolated antibody that binds to CD
154. It also claims a pharmaceutical composition comprising an anti-CD154 antibody and an antiviral agent (e.g., remdesivir) to treat immune-related disease (e.g. COVID-19). However, no data of the composition of remdesivir and the claimed antibody has been disclosed in this patent application [65].

CN11235625A claims the use of lysozyme or a combination comprising lysozyme to prepare medicine or food for preventing or treating COVID-19. The lysozyme may be combined with an antiviral agent (remdesivir) and glycyrhyrrhizic acid. The composition can be administered in an oral dosage form, injection dosage form, and inhalation dosage form. The patent application exemplifies the application of lysozyme in patients with new coronary pneumonia and high-risk infections, but without remdesivir [66].

Our search also revealed many Chinese patent applications and one US patent application related to the preparation of remdesivir, its intermediates, and pharmaceutical impurities. The list of these patent application include CN111393478A [67], CN112358504A [68], CN1112321589A [69], CN112321642A [70], CN112279855A [71], CN111961079A [72], CN111848679A [73], CN111875638A [74], CN111793101A [75], CN111732618A [76], CN111484337A [77], CN111471070A [78], CN111470946A [79], CN111440215A [80], CN11139243A [81], CN11139324A [82], CN111269263A [83], CN111233931A [84], CN111233930A [85], CN111233870A [86], CN111233869A [87], CN111205327A [88], CN111187269A [89], CN111117078A [90], CN11116656A [91], CN112679542A [92], CN112645982A [93], CN122904707U [94], CN112592348A [95], CN122318228U [96], CN112250429A [97], CN112500417A [98], CN114257215A [99], CN112358513A [100], CN112902033A [101], and US2021161927A1 [102]. The economic route of synthesis is vital to drop and control the market price of a therapeutic agent. Accordingly, the authors trust that these patent applications may be helpful to the pharmaceutical scientists/chemists involved in the design of an economical synthetic route to prepare remdesivir.

Discussion

COVID-19, a novel pandemic disease, has been a global problem since December 2019. Countries worldwide have fallen into panic due to its infectious/transmissible nature and lack of proper treatments. Most COVID-19 patients are treated based on the severity of cases, symptoms, and supportive care. This is because of the availability of a few medicines. Scientists are dedicated to identifying appropriate treatment for this pandemic to treat and control its spread. For example, the drug repurposing approach has been utilized to develop an effective treatment for COVID-19, wherein azithromycin, baricitinib, and favipiravir (already approved in some countries) are in clinical trials in the USA [103]. The pharmaceutical industries, including Pfizer, Astra Zeneca, Johnson & Johnson, and Moderna, have developed vaccines for COVID-19 [104].

The development of remdesivir, a broad-spectrum antiviral agent, has been a breakthrough for COVID-19 treatment. It is the first approved treatment for COVID-19 that is clinically used in about 50 countries [12]. The generic structure of remdesivir was first disclosed in WO2009132123A1 [105] to treat hepatitis C, dengue, and Flaviviridae virus infections. WO2009132123A1 [105] is a family member of US8316882B2 [28] and USRE46762E [29] that have already been discussed. Later, it was reported to possess activity against corona infections [33]. Gilead Sciences has developed remdesivir as a freeze-dried preparation for injection. The drug has to be prepared fresh and injected under the supervision of professionals [11], which leads to poor patient compliance. Further, the freshly prepared injection is not stable for an extended period [40]. Therefore, novel compositions of remdesivir with improved patient compliance, safety, stability, and bioavailability have been invented. These include soft gel capsules [33], charcoal-based drug delivery systems [36], fast-dissolving oral film of remdesivir [37], and film-coated tablets [38]. The marketed freeze-dried powder for injection contains SBECO to enhance the aqueous solubility of remdesivir. However, the solubilization process is optimal at a pH<4. On the other hand, remdesivir is unstable in an acidic aqueous solution. Accordingly, the marketed freeze-dried powder for injection also contains pH regulators (hydrochloric acid and sodium hydroxide) [39]. Therefore, the preparation of the freeze-dried powder for injection is a complex process. Further, at the time of injection, remdesivir injection is acidic, which causes poor patient compliance. Accordingly, a new stable, safe, and patient compliant injection of remdesivir in non-aqueous solvent (absolute ethanol and polysorbate) having a short production process has been invented [39]. The non-aqueous injection is also safe for the kidney, unlike SBECO based injection, which causes renal dysfunction [8].

The development of new delivery systems is directed to improve the biological effect and bioavailability of a drug; improve patient compliance; reduce the side effects of the drug, and solve solubility and biodistribution [106]. Accordingly, new spray [48] and nebulizer preparations [49] of remdesivir have been invented to address its side effects and improve its biological action. A stable and effective sublingual tablet of remdesivir having quality pharmaceutical properties has also been invented [41]. Such tablets increase patient compliance in comparison to the marketed injectable formulation of remdesivir. Remdesivir based masks [50] and cosmetics [53] have also been developed that help to prevent the spread of COVID-19. Some patents related to the combinations of remdesivir and other drugs, for example, cell pathway inhibitors (i.e., anti-inflammatory agents) [42], pyrimidine compound [43], isoxazoline parasiticides [44], azithromycin [45,47], and viral protease inhibitory polyepptide [46] have been identified. Such combinations have revealed the synergistic effects against COVID-19 compared to the monotherapy of remdesivir. Many combinations of remdesivir are in a clinical trial also [19]. The development of further inventive composition (monotherapy, combinations, and delivery systems) is anticipated to tackle this disaster of the century.

Remdesivir was first developed to treat Ebola infection. A patent has been granted for the use of remdesivir to treat Ebola infection [54]. Some patents/applications have been located that claim the use of remdesivir to treat different diseases that include cardiovascular complications of diabetes [56], cardiotoxicity caused by the anti-tumor drugs [57], idiopathic pulmonary fibrosis [58], and hepatitis B virus (HBV) [59]. The clinical trial information of remdesivir for its new conditions has been provided in Table 2.

The compound patents of remdesivir are supposed to expire in October 2035. Gilead Sciences has also applied for the legal PTE (that may be up to five years) for its compound patents [31,32]. The extension grant will extend the patent protection of remdesivir till October 2040 in many countries. The generic version of remdesivir may not be available to the patient by 2035–2040 in many countries. Accordingly, it is compulsory to look for alternative therapies also e.g. drug repurposing of the existing therapeutic agents.

Conclusion

The patent literature has revealed inventive compositions, combinations, delivery systems, and new indications of remdesivir. The primary inventions of remdesivir (compositions, combinations, and delivery systems) have been developed to provide synergistic treatment for COVID-19 and patient compliance. Some exciting innovations have also been disclosed to prevent COVID-19, for example, remdesivir based lipstick, masks, sprays, and nebulizers.
The inventions related to new indications of remdesivir increase its therapeutic scope. It is expected that the scientific fraternity will create new ideas based on this review to combat COVID-19.

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Competing interests

None declared.

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