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MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
pharmaceutical faculty
pharmaceutical chemistry department

QUALIFICATION WORK

on the topic: **«SELECTION OF ANALYTICAL METHODS OF REMDESIVIR DETERMINATION IN A SUBSTANCE AND PHARMACEUTICAL PRODUCTS»**

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ANNOTATION

The work reviews and compares spectrophotometric and chromatographic methods for the analysis of remdesivir with an emphasis on their analytical efficiency and environmental friendliness. Practical recommendations for improving the quality control strategies for remedivir in the composition of substances and finished products in accordance with the standards of regulatory authorities are proposed.

The work consists of an introduction, three chapters, general conclusions, and a list of references composed of 47 sources. The content is presented across 55 pages, including 4 tables, 4 figures and 4 schemas.

Key words: remdesivir, spectrophotometry, chromatography, HPLC, quality control, Eco-Scale, pharmaceutical analysis

АНОТАЦІЯ

У роботі розглядаються та порівнюються спектрофотометричні та хроматографічні методи аналізу ремдесивіру з акцентом на їхню аналітичну ефективність та екологічність. Запропоновано практичні рекомендації щодо вдосконалення стратегій контролю якості ремседивіру в складі субстанцій та готової продукції, згідно дотримання стандартів регуляторних органів.

Робота складається зі вступу, трьох розділів, загальних висновків та списку використаних джерел, що налічує 47 найменувань. Зміст роботи викладено на 55 сторінках і містить 4 таблиці, 4 рисунки та 4 схеми.

Ключові слова: ремдесивір, спектрофотометрія, хроматографія, ВЕРХ, контроль якості, Eco-Scale, фармацевтичний аналіз

CONTENT

List of abbreviations

API – Active Pharmaceutical Ingredient

CES1 - carboxylesterase 1

eGFR - estimated glomerular filtration rate

GAC - green analytical chemistry

HPLC - high performance liquid chromatography

LOD - limit of detection

LOQ - limit of quantification

MoGAPI - modified green analytical procedure index

OATP1B1 - organic anion transporting polypeptide 1B1

P-gp - P-glycoprotein

SBECD - sulfo-butyl-ether β-cyclodextrin sodium

TLC - thin-layer chromatography

UV – Ultraviolet

WHO – World Health Organization

INTRODUCTION

Actuality of topic. The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has significantly impacted global healthcare systems, highlighting the urgent need for effective antiviral therapies. Remdesivir, a nucleotide analog prodrug developed originally for the treatment of Ebola virus disease, has emerged as a promising therapeutic agent against SARS-CoV-2. Its rapid approval for emergency use and subsequent clinical applications underline the crucial role of antiviral agents in pandemic preparedness and response.

Remdesivir operates through the inhibition of viral RNA-dependent RNA polymerase, thereby preventing viral replication. The drug's therapeutic efficacy, pharmacokinetic profile, and broad-spectrum antiviral activity have placed it at the center of research and clinical practice during the COVID-19 crisis. As with any pharmaceutical agent intended for critical therapeutic indications, ensuring the quality, purity, and stability of remdesivir is vital for maintaining therapeutic effectiveness and patient safety.

The relevance of developing and improving analytical methods for remdesivir lies in several key aspects:

– Efficacy and safety assurance: Reliable identification and quantification methods are critical to guarantee the therapeutic effectiveness and minimize potential side effects associated with the use of remdesivir.

– Detection of impurities and degradation products: As remdesivir is a chemically complex molecule, it is susceptible to degradation; therefore, robust methods are required for monitoring its stability and detecting any impurities.

– Compliance with regulatory requirements: Analytical methods must comply with stringent international regulatory standards, including those set by pharmacopeias and organizations such as the FDA and EMA.

– Ensuring market competitiveness: Pharmaceutical companies must establish validated, high-performance analytical procedures to meet global quality

standards and maintain competitiveness in the pharmaceutical market.

Currently, monographs for remdesivir are included in leading international pharmacopoeias; however, there remains a continuous need for the development of modern, environmentally sustainable analytical methods that combine high sensitivity, reproducibility, and cost-effectiveness. In this context, the comparative evaluation of spectrophotometric and chromatographic methods for remdesivir analysis represents an urgent and relevant scientific task aimed at optimizing quality control procedures.

Purpose of work is to carry out a comparative assessment of modern existing methods of analysis for the tasks of pharmaceutical analysis of remdesivir in pharmaceutical substances and finished products.

Tasks of the research:

– to review the scientific literature on the pharmacological properties, pharmacokinetics, and synthesis of remdesivir;

– to analyze modern methods used for the identification and quality control of remdesivir;

– to evaluate the advantages and disadvantages of spectrophotometric and chromatographic methods applied to remdesivir analysis;

– to perform a comparative analysis of methods based on key parameters such as sensitivity, linearity, detection limits, and environmental impact;

– to assess the environmental sustainability of analytical methods using MoGAPI tools;

– to recommend suitable analytical strategies for routine quality control and regulatory compliance of remdesivir-based pharmaceutical products.

The object of the research is remdesivir as a pharmaceutical substance and as an active pharmaceutical ingredient in finished dosage forms intended for parenteral administration.

The subject of the research is the comparative evaluation of

spectrophotometric and chromatographic methods for remdesivir quality control in a substance and pharmaceutical products.

Methods of the research: include spectrophotometry in the infrared region, spectrophotometry in the visible and ultraviolet regions, thin-layer chromatography, high-performance liquid chromatography, and statistical methods for processing experimental data. Eco-Scale and MoGAPI assessment tools were also applied for the evaluation of environmental sustainability.

The practical value of the results. The results of this study can be used to optimize the analytical quality control of remdesivir, providing pharmaceutical manufacturers and quality assurance laboratories with validated recommendations for the selection of appropriate analytical techniques. The work also emphasizes the importance of integrating green analytical chemistry principles into pharmaceutical analysis practices.

Elements of scientific research. Comparative evaluation of different spectrophotometric and chromatographic techniques was performed with special attention to their ecological impact. Recommendations were developed regarding the selection of analytical methods for remdesivir based on the balance between analytical performance and environmental sustainability.

Approbation of the research results and publications. The results of the work were presented in the form of an oral report at the meeting of the student scientific society of the Pharmaceutical Chemistry Department within the XXXI International scientific and practical conference of young scientists and students “Actual issues of creating new drugs” (23-25 April 2025, NUPh, Kharkiv).

Structure and scope of the qualification work. The work consists of an introduction, three chapters, general conclusions, and a list of references composed of 47 sources. The content is presented across 55 pages, including 4 tables, 4 figures and 4 schemas.

CHAPTER I
PHARMACOLOGY PROPERTIES OF REMDESIVIR

The new global coronavirus disease 2019 (COVID-19) is mainly caused by the severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]. COVID-19 caused severe catastrophic impact on the world's population, resulting in more than 3.8 million deaths worldwide. SARS-CoV-2 is spreading rapidly across the world after the first case of this viral disease was demonstrated in Wuhan, Hubei Province, China, in late December 2019. This promoted the WHO to declare a global pandemic on March 11, 2020 [1, 2]. The rapid spread and devastating effects of COVID-19 promoted researchers around the world to discover antiviral drugs that could control the spread of the virus and help patients recover more quickly. Because the process to approve a novel drug for human use is lengthy and involves numerous phases to collect safety data and identify potential hazards, the easiest and fastest option was to use FDA-approved drugs such as favipiravir, remdesivir and lopinavir / ritonavir [3].

Remdesivir is a nucleotide prodrug of an adenosine analog. It binds to viral RNA-dependent RNA polymerase and inhibits viral replication by premature termination of RNA transcription. Remdesivir has shown activity against SARS-CoV-2 in vitro. Intravenous remdesivir is approved by the FDA for the treatment of COVID−19 in hospitalized adult and pediatric patients (aged ≥ 12 years and weighing ≥ 40 kg). It is also available via European emergency approval for the treatment of COVID−19 in hospitalized pediatric patients weighing 3.5 kg to more than 40 kg or for patients younger than twelve years with a weight of no less than 3.5 kg [4]. It should be administered in a hospital or health care facility that can provide a similar level of care as an inpatient hospital [5].

1.1. ADME properties of remdesivir

1.1.1. Absorption

Remdesivir is available in two pharmaceutical forms: a solution and a lyophilized powder. The solution is prepared at a concentration of 5 mg/mL, packaged in a 100 mg/20 mL vial, while the lyophilized powder comes in a single-dose vial containing 100 mg. The powder formulation requires reconstitution with either 0.9% saline or a 5% glucose solution before administration. The preferred method of delivery is intravenous infusion, typically lasting between 30 and 120 minutes.

For adult patients, the standard dosing regimen consists of an initial intravenous loading dose of 200 mg on the first day, followed by daily maintenance doses of 100 mg for a duration of either 2–5 days or up to 10 days, depending on clinical need. Intravenous administration is favored due to its ability to ensure 100% bioavailability. Oral administration is not suitable because remdesivir undergoes extensive first-pass metabolism via hydrolysis in the gastrointestinal tract, leading to minimal systemic absorption [6].

To enhance intracellular concentrations of remdesivir triphosphate, the drug has been developed as a prodrug. While intramuscular injection offers better absorption than oral administration, it still results in subtherapeutic levels due to the slow release of the drug from muscle tissue, which keeps systemic concentrations below the desired range. Currently, an inhaled formulation of remdesivir is under investigation, as SARS-CoV-2 primarily affects the lungs. It is believed that inhalation could provide effective local drug delivery directly to the primary site of infection. This formulation is mainly intended for outpatient treatment and patients with mild to moderate COVID-19 [7].

After slow intravenous infusion, remdesivir diffuses across the cell membrane and undergoes a series of hydrolysis reactions within the cytosol. The conversion of its nucleoside core (GS-441524) results in a water-soluble

monophosphate form that remains trapped inside infected cells, preventing its efflux. This mechanism ensures efficient cellular uptake of remdesivir when administered as a slow IV infusion [8].

In addition to its formulation and route of administration, remdesivir absorption is influenced by transport proteins. It serves as a substrate for P-glycoprotein (P-gp) and organic anion transporting polypeptide 1B1 (OATP1B1) transporters. Additionally, its alanine metabolite is recognized by both OATP1B1 and OATP1B3. The expression levels of these transporters on the cell membrane play a crucial role in drug disposition, as P-gp can actively transport remdesivir out of cells, reducing its intracellular concentration and therapeutic effectiveness [9].

1.1.2. Distribution

Following intravenous administration, remdesivir reaches tissues and blood cells through passive diffusion. The parent drug exhibits a relatively strong affinity for human plasma proteins, with a binding rate of 88.0–93.6%, whereas GS-441524 and GS-704277 demonstrate significantly lower binding at 2% and 1%, respectively. Due to its instability in tissues, remdesivir is expected to have limited tissue distribution. However, once its active metabolite enters the cells, it accumulates to a greater extent compared to its extracellular prodrug form [10].

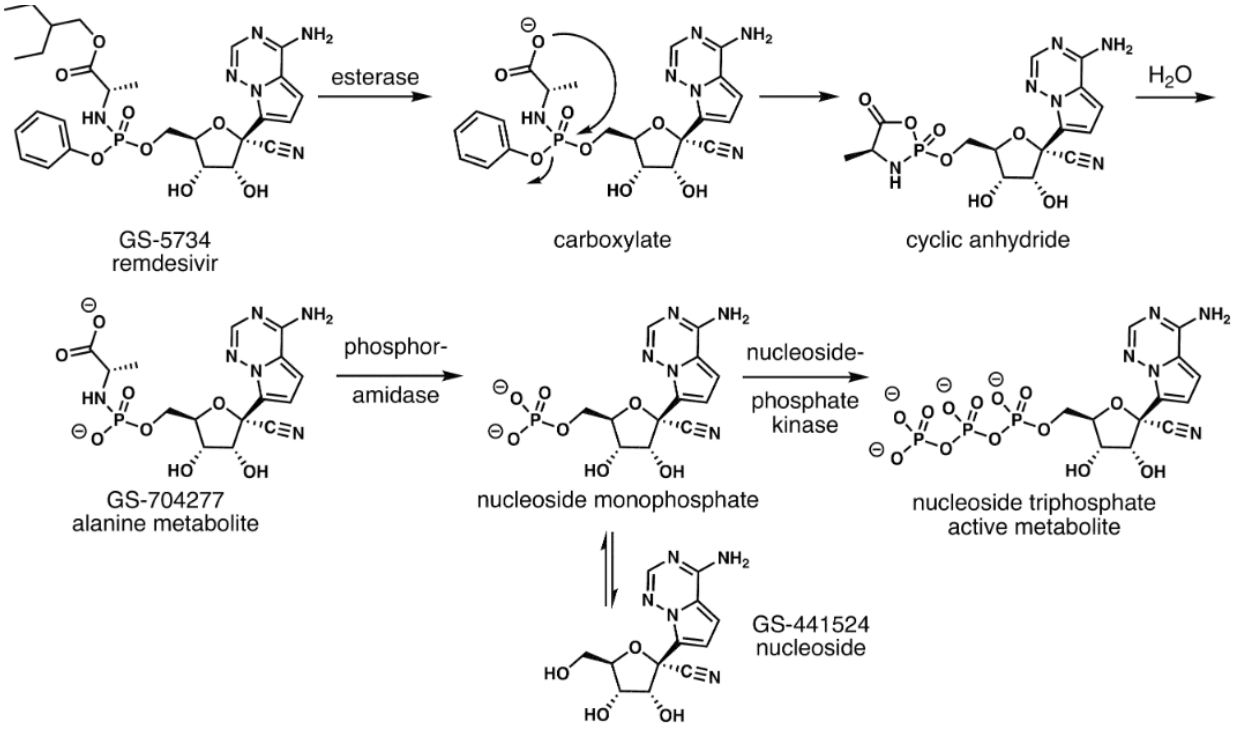
In a study involving eight participants, remdesivir demonstrated a volume of distribution ranging from 45.1 to 73.4 L when administered in single doses between 10 mg and 225 mg. Likewise, in a multiple-dose study (150 mg/day) conducted over 7 or 14 days, the volume of distribution was reported as 85.5 L. To assess remdesivir's cellular distribution, the intracellular concentrations of GS-441524 (nucleoside core) and GS-443902 (active triphosphate) in peripheral blood mononuclear cells were measured. Notably, these concentrations were found to be 220 to 370 times higher than the EC50 for SARS-CoV-2 [11].

Animal studies in rats and monkeys indicate that remdesivir has limited distribution across most tissues, with minimal or no presence detected in the brain, suggesting poor penetration of the blood–brain barrier. This implies that achieving

effective concentrations in infected organs may require higher or more frequent dosing. However, doses exceeding 200 mg have been associated with increased risks of hepatotoxicity and renal impairment. Given these concerns, further research into an inhaled formulation of remdesivir is warranted to optimize drug delivery to infected cells while minimizing systemic toxicity and adverse effects [12].

1.1.3. Metabolism

Remdesivir (GS-5734) is an adenosine analog prodrug that is converted first to the alanine metabolite (GS-704277) and then to the nucleoside core (GS-441524) [13].



Scheme 1.1. Activation of remdesivir into its active triphosphate metabolite [14]

Remdesivir is a prodrug that undergoes hydrolysis to convert into its active triphosphate form, GS-443902 [15]. This biotransformation primarily involves carboxylesterase 1 (CES1), accounting for 80% of the metabolism, while cathepsin A and CYP3A contribute approximately 10% each. Additionally, in vitro studies suggest that CYP2C8 and CYP2D6 play a minor role in remdesivir metabolism.

Another metabolite, GS-704277, is processed by Histidine Triad Nucleotide-binding Protein 1. The majority of remdesivir's metabolites (74%) are excreted through urine, while around 18% are eliminated via feces. The predominant remdesivir-derived compound found in urine is GS-441524, whereas only 10% of the parent prodrug remains detectable [16].

The hepatic clearance of remdesivir is primarily governed by liver blood flow rather than metabolic enzymes. This assumption is based on its high extraction ratio and relatively short elimination half-life [17].

1.1.4. Elimination

The primary remdesivir-derived compound found in urine is its nucleoside core, GS-441524, while the parent drug and other metabolites are present at moderate to low levels. The elimination of remdesivir and its alanine metabolite (GS-704277) primarily occurs through biotransformation, whereas GS-441524 is cleared via renal pathways, including glomerular filtration and active tubular secretion. Around 10% of remdesivir is excreted in urine as a metabolite, whereas 49% of the administered dose is eliminated as GS-441524 [18].

Neither remdesivir nor its alanine metabolite has been detected in feces, and less than 1% of the dose is excreted as GS-441524 in fecal matter. The half-life of GS-441524 is approximately 27 hours, compared to 1 hour for remdesivir and 1.3 hours for GS-704277. The intracellular nucleoside triphosphate form of remdesivir has a half-life ranging between 14 and 24 hours, while its plasma half-life is about 1 hour. Due to the anionic charge of the molecule, the nucleoside triphosphate remains within the cellular compartment for an extended period. This prolonged intracellular half-life allows for once-daily dosing of remdesivir [19].

Since renal clearance is the primary route of elimination, remdesivir is not recommended for patients with significant renal impairment or those undergoing renal replacement therapies such as dialysis or hemodialysis. Patients with an estimated glomerular filtration rate of 30 mL/min or higher can receive remdesivir

without dose adjustments. However, if estimated glomerular filtration rate falls below 30 mL/min, its use is no longer advised [20].

1.2. Pharmacology

1.2.1. Pharmacodynamic properties

Remdesivir is activated inside cells to produce GS-443902, an adenosine triphosphate analog that broadly inhibits viral RNA polymerases. The activation occurs through hydrolase cleavage by carboxylesterases, forming the intermediate metabolite GS-704277. After breaking the phosphoramidate bond, the nucleoside analogue monophosphate, GS-441524-MP, is generated and subsequently phosphorylated to yield the active nucleoside triphosphate, GS-443902. When GS-441524-MP is dephosphorylated, it converts to GS-441524, which is less effective for re-phosphorylation. Remdesivir and its metabolites (GS-704277 and GS-441524) are detectable in plasma, while the active triphosphate GS-443902 is only found intracellularly, with peripheral blood mononuclear cells (PBMCs) used as a surrogate for measuring its activation [21].

1.2.2. Pharmacokinetic properties

The pharmacokinetics of remdesivir, its nucleoside core (GS-441524), and alanine metabolite (GS-704277) have been explored in a limited number of clinical studies. One study involved two severely infected COVID-19 patients receiving a loading dose of 200 mg/day of remdesivir, followed by 100 mg/day for 12 days. Another trial with healthy volunteers used the same dosing regimen. Both studies found that remdesivir and GS-441524 reached peak concentrations within 1 hour, with remdesivir achieving a peak serum concentration of 3027 ng/mL immediately after IV infusion, followed by a rapid decline. The area under the curve for remdesivir over 24 hours ranged from 2.9 to 4.0 μg h/mL. In patients, plasma concentrations of GS-441524 ranged from 214 ng/mL to 316 ng/mL at 1 and 4 hours post-infusion, with an area under the curve of 3.11 to 6.13 μg h/mL after 24

hours. The C_{max} of remdesivir on days 1 and 5 was 5.44 μg/mL and 2.61 μg/mL, while GS-441524's C_{max} was 0.15 μg/mL and 0.14 μg/mL, respectively.

Healthy participants were tested with remdesivir dosages from 3 mg to 225 mg in a complete dose escalation trial, showing a linear kinetics profile. After a single dose, Cmax varied from 57.5 ng/mL to 4420 ng/mL, requiring 2 hours to reach peak concentration. The area under the curve ranged from 67.1 ng/mL to 5260 ng/mL, with clearance and volume of distribution varying accordingly. Active triphosphate concentrations were significantly higher after IV administration compared to in vitro EC_{50} values.

Knowledge of remdesivir pharmacokinetic in specific populations, such as patients with renal or hepatic impairment, remains limited. In silico modeling indicates that distribution is influenced by age, weight, and organ function. Due to renal elimination, data on patients with renal impairment is necessary, as plasma concentrations are higher in those with chronic kidney disease. The FDA advises against using Remdesivir in patients with an eGFR below 30 mL/min. Acute kidney injury was a common side effect in clinical studies, potentially linked to the solubility enhancer sulfobutylether-cyclodextrin sodium present in Remdesivir formulations. Despite its renal toxicity, sulfobutylether-cyclodextrin does not appear to cause significant damage in compromised patients, but kidney function should still be monitored during treatment.

Additionally, remdesivir has shown potential in reducing the inflammatory response in mice with non-alcoholic fatty liver disease, potentially benefiting obese COVID-19 patients with liver disease. This suggests that remdesivir may influence treatment outcomes and safety for this population [22].

1.3. Side effects

Adverse event (≤5%) observed in 4 Phase-1, blinded-studies conducted with remdesivir (n = 138) in healthy individuals include phlebitis, constipation, headache, ecchymosis, nausea and pain in the extremities [23].

The common adverse event noted during compassionate use of remdesivir in patients with COVID-19 include rash, diarrhea, hypotension, abnormal liver function and renal impairment. Serious adverse events (acute kidney injury, septic shock, multi-organ failure) was noted in 23%, while 60% had at least one adverse event and 8% discontinued due to various side effect of remdesivir [24]. Although serious adverse events reported in 18% vs. 26% in remdesivir vs. control arm respectively; more patients from the remdesivir group discontinued remdesivir (12%), compared to the control arm (5%) either because of adverse events or serious adverse events (notably, 5% in remdesivir group had acute respiratory distress syndrome or respiratory failure). The most common adverse events noted in SIMPLE trial occurring in more than 10% of patients in either group were nausea (10.0% vs. 8.6%, 5-days vs. 10-days group, respectively) and acute respiratory failure (6.0% vs.10.7%, 5-days vs. 10-days group, respectively). Grade 3 or higher liver enzyme elevations occurred in 7.3% of patients, while 5% in 5-days arm and 10% in 10-days arm had to withdraw from remdesivir due to severe adverse events [25].

In non-clinical reproductive toxicity studies, no adverse effect on embryo-fetal development in pregnant animal or male infertility were observed with remdesivir, however at a systematically toxic dose an embryonic toxicity was seen. Remdesivir has not been studied in pregnancy, lactating women and pediatric population. Interestingly, in a randomized controlled trial named The Pamoja Tulinde Maisha study of acute Ebola virus disease, 3% of pregnant women and 26% of children received remdesivir, without any notable side effects [26].

Although no signs of nephrotoxicity have been observed in healthy individuals, the use of remdesivir requires caution. The lyophilized and solution formulations of remdesivir at a 150 mg dose contain 4.5 g and 9.0 g of sulfo-butyl-ether β-cyclodextrin sodium (SBECD), respectively, while the maximum recommended daily dose of SBECD is approximately 250 mg/kg, according to the European medicines agency safety review. SBECD is included in the formulation

as a solubilizing agent due to the limited aqueous solubility of remdesivir. Since SBECD is eliminated through the kidneys, individuals with moderate to severe renal impairment may experience increased systemic exposure to this compound. Therefore, careful monitoring of estimated glomerular filtration rate (eGFR) is essential when administering remdesivir, particularly in patients with pre-existing renal dysfunction, and discontinuation is required if eGFR declines by ≥50% from baseline.

Although the parent drug, remdesivir, undergoes minimal renal excretion, its active metabolite GS-441524 is found in urine at levels reaching 49%, which suggests that impaired renal function could theoretically increase plasma exposure to this metabolite. Nevertheless, considering the benefit-risk ratio in patients with COVID-19, no dose adjustment is currently recommended for those with mild to moderate renal impairment. However, the use of remdesivir is contraindicated in patients with severe renal dysfunction (eGFR <30 ml/min). It is important to note that no specific studies have been conducted to evaluate the safety of remdesivir in patients with renal impairment [23].

Conclusion to Chapter I

1. Remdesivir is a nucleotide prodrug of an adenosine analog that inhibits the SARS-CoV-2 RNA-dependent RNA polymerase, thereby halting viral replication. It demonstrates significant antiviral activity and has been approved for emergency use in treating moderate to severe cases of COVID-19. Its clinical effectiveness is supported by pharmacodynamic data showing potent intracellular activity.

2. Due to extensive first-pass metabolism, remdesivir is administered intravenously to ensure 100% bioavailability. It is converted intracellularly into its active triphosphate form, GS-443902, through a sequence of enzymatic reactions, resulting in sustained intracellular retention and once-daily dosing capability.

3. Remdesivir shows high plasma protein binding but limited tissue distribution. Its primary elimination pathway is renal, predominantly in the form of its metabolite GS-441524. Clearance is influenced by glomerular filtration and active secretion mechanisms.

4. Although remdesivir is generally well tolerated, common adverse effects include gastrointestinal disturbances, liver enzyme elevations, and potential nephrotoxicity. These risks are especially relevant in patients with impaired kidney function due to the accumulation of the excipient SBECD (sulfo-butyl-ether β-cyclodextrin sodium).

5. Pharmacokinetics vary depending on age, weight, renal function, and co-existing conditions. Limited data exist for special populations such as pregnant women and pediatric patients, indicating a need for further clinical research.

CHAPTER II
PHYSICO-CHEMICAL PROPERTIES AND MODERN METHODS OF ANALYSIS OF REMDESIVIR

2.1. Synthesis and physico-chemical properties of remdesivir

Remdesivir

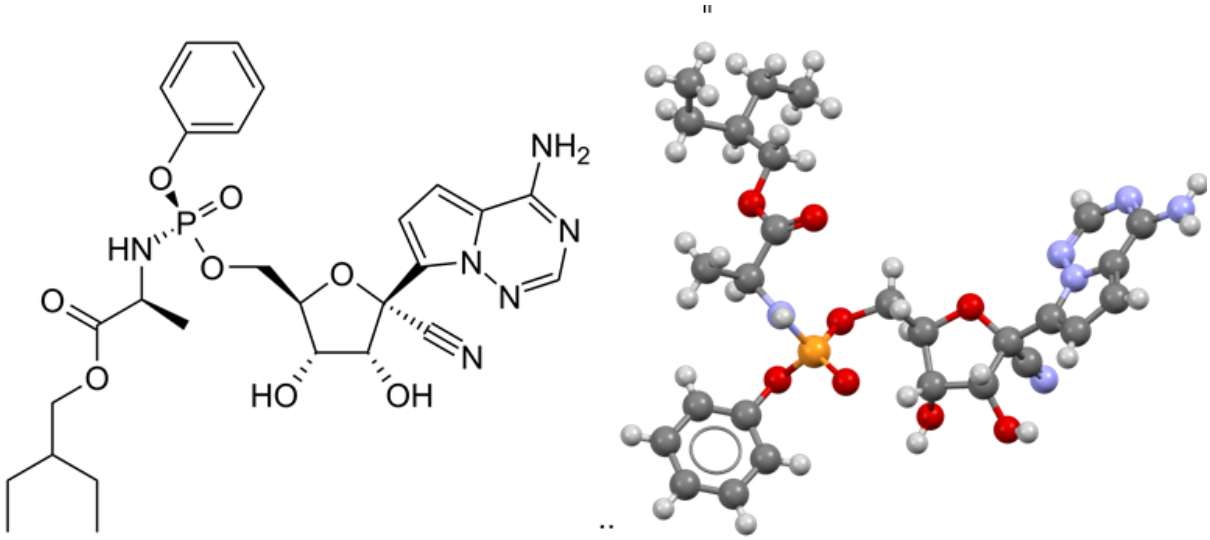


Figure 2.1. Chemical structure of remdesivir

IUPAC name is 2-Ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl] amino}propanoate

Molecular formula is $C_{27}H_{35}N_6O_8P$.

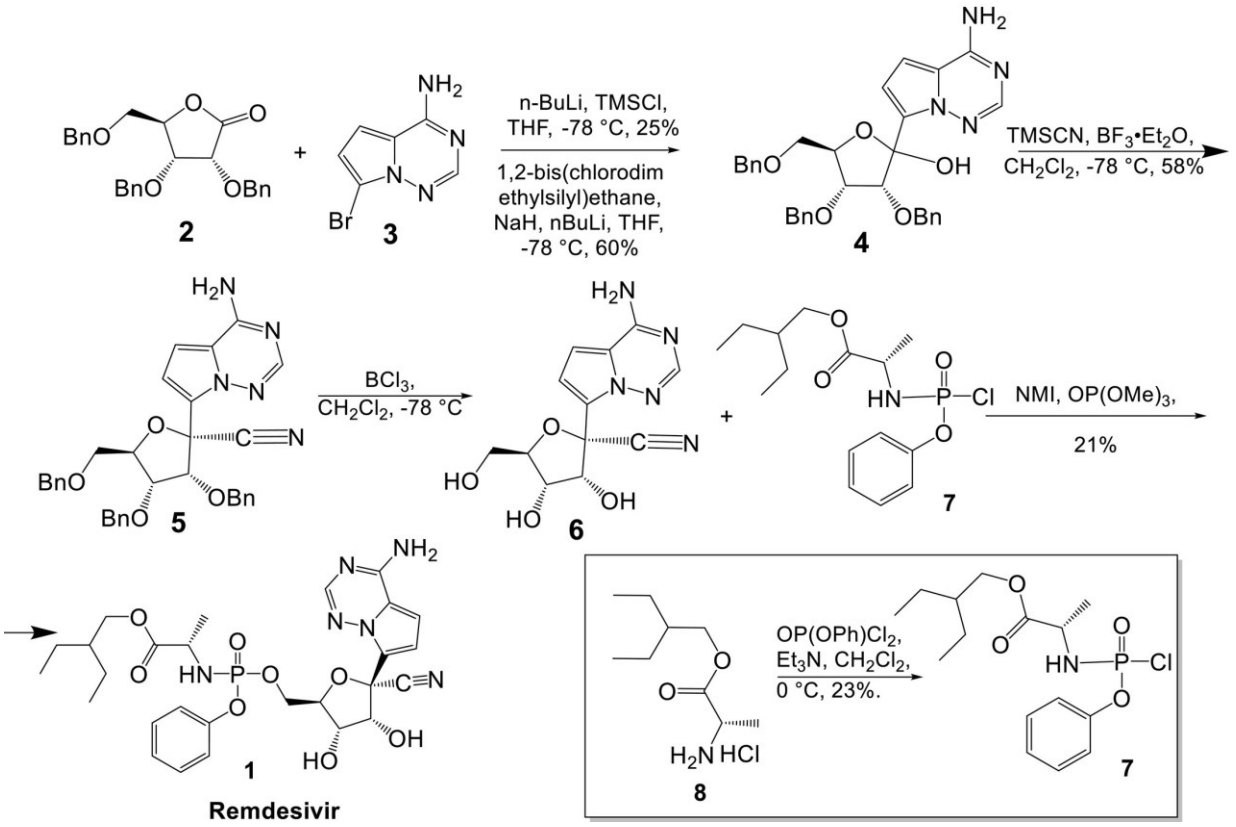
Molecular weight is 602,6 g/mol.

Remdesivir is a solid compound that ranges in color from white to off-white or yellow and is non-hygroscopic. It is soluble in ethanol and freely soluble in methanol and dimethylsulfoxide. It is practically insoluble in water.

The molecule possesses six chiral centers and is synthesized as a single stereoisomer. Various polymorphic forms of remdesivir exist, with the active pharmaceutical ingredient primarily produced as Form II or as a mixture of Form II with another crystalline form. Both the pure Form II and the mixed polymorphic

forms exhibit comparable solubility, ensuring no significant impact on the performance of the final drug product. Before intravenous administration, the active substance must be dissolved in solution.

Siegel et al. [27] developed a single *Sp* phosphoramidate prodrug, remdesivir, through glycosylation of compound 6. This involved metal-halogen exchange of bromo-base 3, followed by its addition to ribolactone 2 (Scheme 2.1).



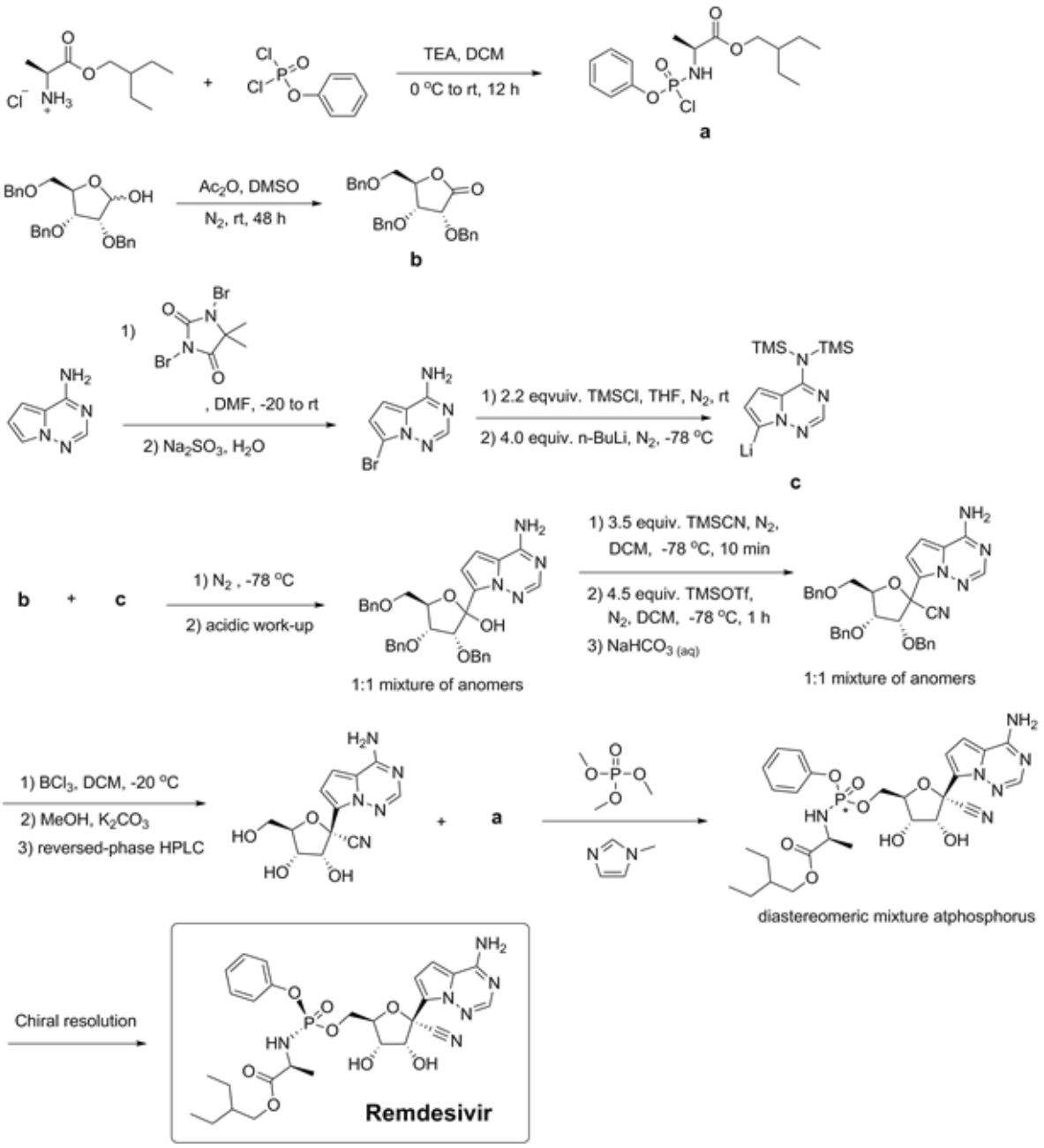
Scheme 2.1. Siegel route for synthesis of remdesivir.

Two conditions were tested for C-C bond formation. In the first, *n*-BuLi and TMSCl facilitated lithium-halogen exchange and silyl protection, yielding compound 4 (25%). The second used NaH and 1,2-bis(chlorodimethylsilyl)ethane for protection before lithium-halogen exchange, improving the yield to 60%. Both methods were inconsistent due to sensitivity to cryogenic conditions and *n*-BuLi addition rates.

Compound 4, a mixture of 1′-isomers, underwent 1′-cyanation to yield *α*-anomer 5. After benzyl group removal, compound 6 was obtained. The final

phosphoramidoyl chloridate prodrug moiety 7 was conjugated to form 1a as a 1:1 diastereomeric mixture (21% yield) [28].

Remdesivir can be synthesized in multiple steps from ribose derivatives. The figure to the right is one of the synthesis routes of remdesivir invented by Chun and coauthors from Gilead Sciences (scheme 2.2.) [29, 30].

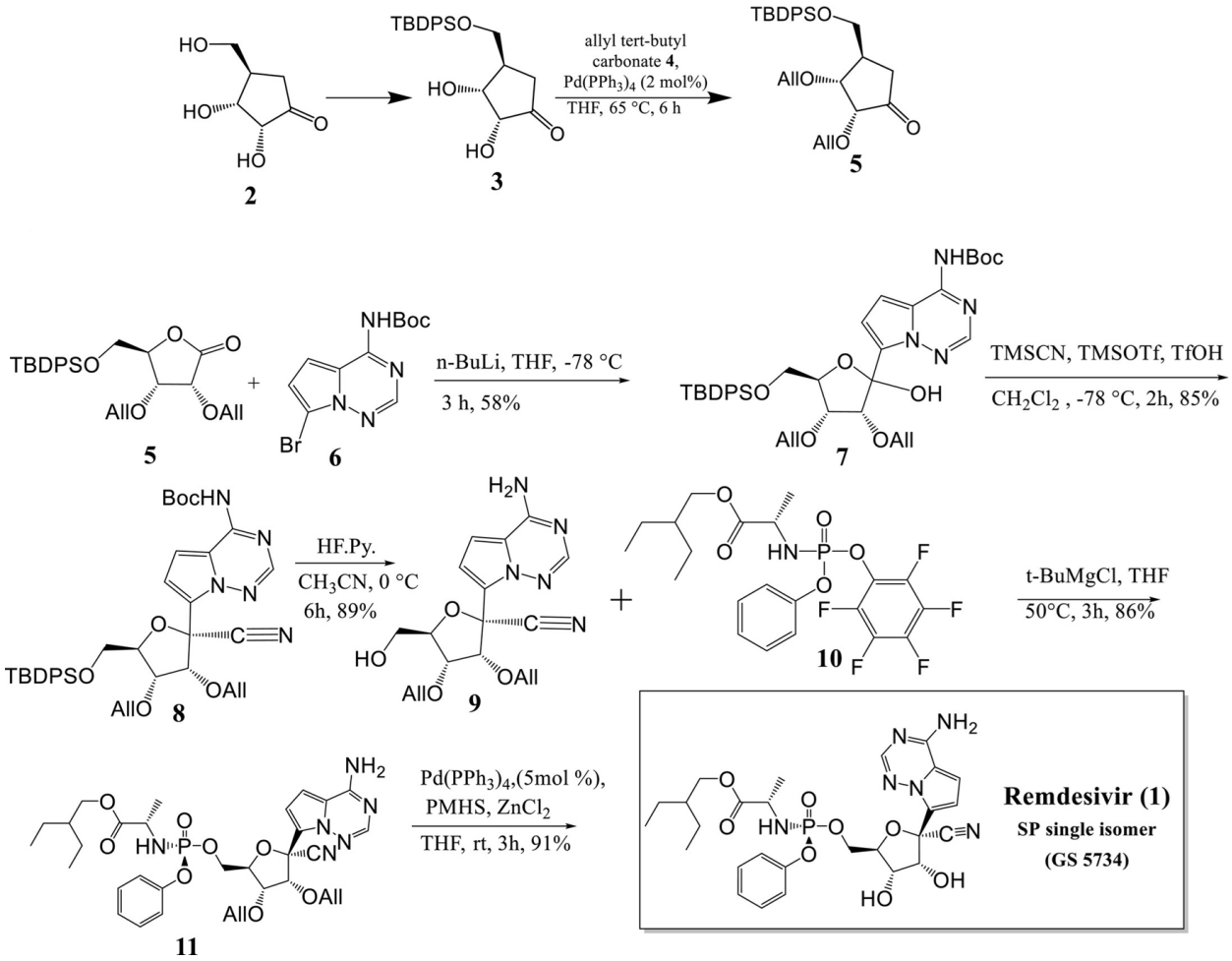


Scheme 2.2 Gilead route for the synthesis of remdesivir

Kumar Palli et al. [31] developed a concise seven-step synthesis of remdesivir with a total yield of 25%, starting from *d*-ribonolactone 2 (Scheme 2.3).

Initially, the primary hydroxyl group was protected using TBDPS, yielding silyl ether 3 (84%). Further protection of secondary alcohols with allyl *tert*-butyl carbonate (2 mol% $Pd(PPh_3)_4$) produced diallylated ribonolactone 5 (89%).

Next, lactone 5 underwent C-glycosylation with protected nucleobase 6, yielding an anomeric mixture (2:1) of compound 7 (58%) in the presence of *n*-BuLi. Cyanation of 7 generated cyano-glycoside 8 (85%) with high selectivity (d.r. = 96:4, β:α). Deprotection of silyl and Boc groups using HF·Pyridine gave amino-alcohol 9 (89%). The final key step involved P-chiral phosphorylation, where 9 reacted with chiral pentafluoro-phosphoramidate 10 (*t*-BuMgCl), forming phosphoramidate ester 11 (86%) as a single diastereomer.



Scheme 2.3. Palli route for the synthesis of remdesivir

2.2. Methods of analysis of remdesivir in a substance and medicines

2.2.1. Identity tests

Quantitative analysis of compounds based on the structural properties remains an attractive approach for researchers and chemists. In general, many pharmaceutical compounds have different functional groups which can enable selective quantitative analysis [32].

2.2.1.1. Spectrophotometry in the infrared region

The infrared absorption spectrum is concordant with the spectrum obtained from remdesivir RS or with the reference spectrum of remdesivir (Fig. 2.2) [33].

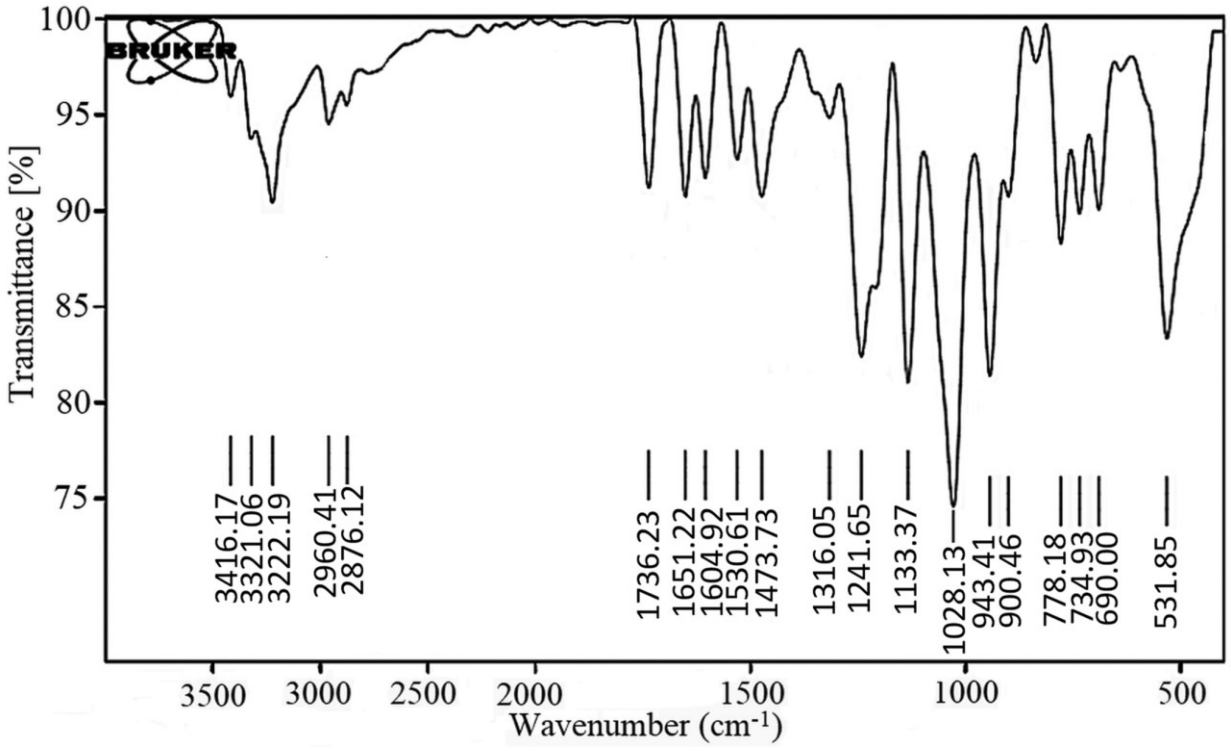


Figure 2.2. Reference IR spectrum of remdesivir.

Table 2.1.

Interpretation of Remdesivir IR -spectra

No.	Functional group	Standard value (cm^{-1})	Obtained value
1	C-O group	1050–1150	1133.37
2	C-N group	1000–1350	1241.65
3	C=C group	1600–1680	1604.92
4	C=O group	1640–1810	1736.23
5	C-H group	2850–3000	2960.41
6	O-H group	2500–3400	3222.19
7	N-H group	3300–3500	3416.17

2.2.1.2. Spectrophotometry in the visible and ultraviolet regions

The ultraviolet absorption spectrum of a methanol solution of remdesivir with a concentration of 20 μg/mL is characterized by the presence of two analytical absorption maxima at 245 nm and 275 nm when observed between 220 nm and 400 nm.

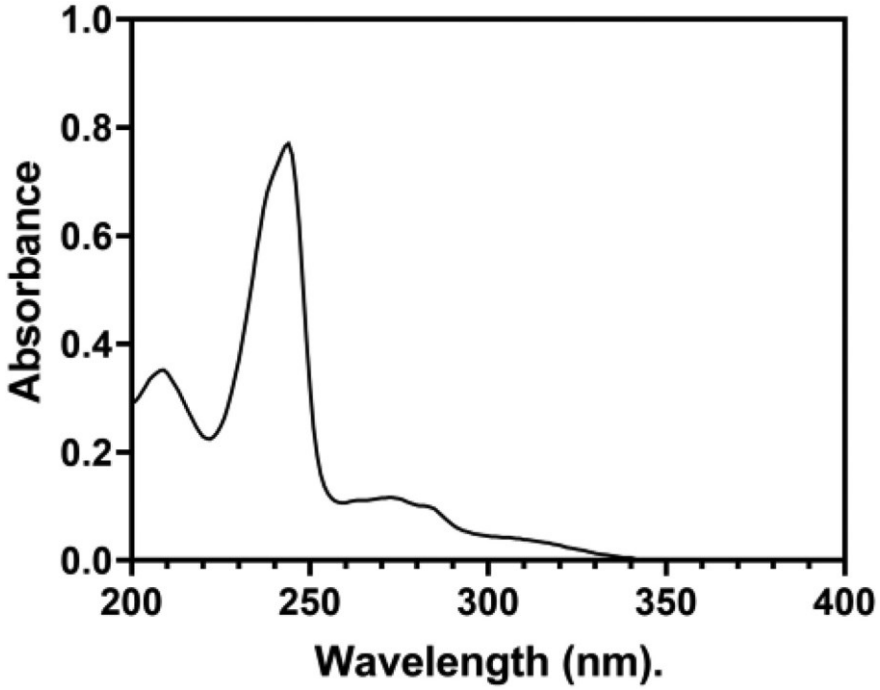


Figure 2.3. Ultraviolet absorption spectrum of methanol solution of remdesivir (20 μg/ml).

2.2.1.3. Thin-layer chromatography

The thin-layer chromatography (TLC) analysis uses silica gel R_6 as the stationary phase and a freshly prepared mobile phase consisting of ethyl acetate R, methanol R, and glacial acetic acid R in a ratio of 90:9:1 (V/V/V).

Onto the TLC plate, 2 µL of each of the following methanolic solutions are applied separately:

- Solution (A): 1 mg of the test substance per mL
- Solution (B): 1 mg of remdesivir RS per mL

After chromatographic development, the plate dries in ambient air or under a gentle airflow. The chromatogram is examined under ultraviolet light at 254 nm. The principal spot in the chromatogram of solution (A) corresponds in position, appearance, and intensity to the remdesivir spot in the chromatogram of solution (B), confirming the identity of the test substance [34]

2.2.1.4. Specific optical rotation

The specific optical rotation of 10.0 mg/ml solution of the test substance in methanol calculated with respect to an anhydrous substance should be in the range from -25.0 to -18.0 [33].

2.2.2. Methods of quantitative determination of API and control of impurities

2.2.2.1. Non-aqueous titration

WHO propose a Remdesivir draft for inclusion for The International Pharmacopoeia [35]. Non-aqueous titration is described method as assay of remdesivir.

To perform the assay, 0.4 g of remdesivir dissolves in 50 mL of glacial acetic acid. Then the solution is titrated with 0.1 mol/L perchloric acid. Each mL of 0.1 mol/L perchloric acid is equivalent to 60.26 mg of remdesivir.

2.2.2.2. Multiple Isothermal Titration Calorimetry

Isothermal titration calorimetry under multiple conditions. Experts from universities in Spain and the USA conducted various isothermal titration

calorimetry experiments in conjunction with computational molecular dynamics simulations. Their aim was to explore the structural and thermodynamic elements of the connection between captisol and either neutral or protonated remdesivir. At a pH of 3, thorough examination of the calorimetric data revealed a robust complex with a high association constant of 10^4. The profiles of the potential mean force indicated that lower association constant values correspond to less tightly bound structures with fewer sulfobutylether substitutions. This finding is in agreement with the results from isothermal titration calorimetry that emphasized how the affinity is notably impacted by both the quantity and positioning of captisol-containing structures [36].

2.2.2.3. High Performance Liquid Chromatography

A range of HPLC methods has been developed for the quantitative and qualitative analysis of Remdesivir, each utilizing unique combinations of mobile phases, column specifications, and operational parameters to enhance method performance. Various mobile phases were employed, including aqueous-organic mixtures with orthophosphoric acid, acetonitrile, methanol, and dimethyl sulfoxide, demonstrating the compound's stability across a wide pH range and solvent systems. C18 columns of different lengths (from 150 to 250 mm) and particle sizes (from 3.5 to 5 µm) were commonly used, with flow rates varying between 0.7 and 1.2 ml/min.

The methods showed considerable variation in sensitivity. The limit of detection (LOD) ranged from 0.0195 µg/ml to 3.00 µg/ml, while the limit of quantification (LOQ) ranged from 0.0649 µg/ml to 9.00 µg/ml. The most sensitive method utilized an acidified water–acetonitrile system (pH 3), achieving the lowest LOD and LOQ. The duration of analysis also differed, from as brief as 10 minutes to as long as 70 minutes, indicating the trade-off between analysis speed and separation efficiency. UV detection wavelengths ranged from 230 to 247 nm, chosen based on the maximum absorbance of the analyte under each set of conditions.

2.3. Greenness Assessment of Analytical Methods for Remdesivir Using the MoGAPI Tool

Green chemistry was created in 1990 to reduce the damage that chemical production does to the environment. Green Analytical Chemistry (GAC), an analytical approach, is based on modified versions of the twelve green chemistry principles. Several standards have been established to assess greenness since the introduction of the Green Accreditation Council in 2000. Each profession, including engineering, pharmacology, and chemistry, uses substances and techniques to evaluate its products. Recently, scientists have focused on developing environmentally friendly analytical procedures employing green chemistry as a means of preventing pollution.

Environmental friendliness and high-quality findings are difficult to balance in analytical chemistry. Anastas and Warner developed twelve GAC principles in 1998 with the goals of lowering waste, utilizing safer chemicals, using less solvent, and improving energy efficiency. For maximum advantage, studies indicate that these principles should be adjusted, and the 12-point framework put out by Anastas and Warner misses important elements. Since the core concept behind "green chemistry" is to reduce environmental risks and enhance public health by minimizing the development, approach, and use of hazardous chemicals through appropriate knowledge, preventing or minimizing the generation of hazardous chemicals is now more important than treating inefficiencies that have already been created. The twelve GAC principles are represented in Fig. 2.4.

Figure 2.4. Twelve principles of green analytical chemistry

In recent years, the implementation of green chemistry principles in pharmaceutical analysis has become a priority, particularly in light of growing environmental concerns and the need for sustainable laboratory practices.

Several tools are currently utilized to estimate the environmental impacts of analytical processes. These metrics include the analytical Eco-Scale, green analytical procedure index (GAPI), and AGREE metric, which are widely employed besides other tools and modifications such as ComplexGAPI and AGREEprep, due to their ease of use and applicability to a wide range of analytical techniques, including UV-vis spectrophotometry, spectrofluorometry, chromatography, and others. According to the Scopus database, the most commonly cited evaluation tools are the analytical Eco-Scale and GAPI, with 937 and 570 documents, respectively [37].

The analytical Eco-Scale assigns a score out of 100 based on several factors, including the nature and quantity of solvents and reagents used, energy consumption, occupational hazards, and waste generation and management [38]. However, it does not consider the severity or hazardous nature of pictograms when assigning hazard penalty points to chemicals. Additionally, it is not yet possible to obtain analytical Eco-Scale results using an online tool. It lacks the visual impact of the GAPI and the AGREE metric. Despite these limitations, the analytical Eco-Scale remains a valuable tool for providing quantitative information about the environmental impact of analytical procedures.

The GAPI evaluates the environmental hazards of the entire analytical methodology using five colored pentagrams for the different steps involved in the analytical methodology. Each pentagram assesses specific aspects of the methodology: sampling, type of method, sample preparation, solvents/reagents used, and energy consumption. The GAPI tool provides a quick and fast overview of the greenness of different steps of the analytical methodology, making it useful for evaluating and optimizing analytical methodologies to reduce environmental effects [39]. However, the GAPI tool does not provide a total score for each procedure to facilitate comparison between methods. This point is the main drawback related to its use, and it may be a possible element that could further limit the diffusion of this tool.

The evaluation of method greenness is especially relevant in the context of antiviral agents such as remdesivir, whose analytical methods often involve complex matrices and the use of organic solvents. To address these challenges, the Modified Green Analytical Procedure Index (MoGAPI) was introduced as an advanced tool for assessing the environmental sustainability of analytical procedures.

MoGAPI builds upon the conventional GAPI tool by combining visual scoring with a quantitative evaluation system, thus providing a more detailed and reliable method assessment. It evaluates key stages of an analytical procedure,

including sample preparation, solvent and reagent use, energy consumption, instrumentation, and waste management. Each criterion is rated on its environmental impact, allowing for a cumulative score that reflects the overall greenness of the method. According to MoGAPI's scoring system, methods scoring above 75% are classified as “excellent green”, those between 50–74% are considered “acceptable green”, while scores below 50% indicate that the method is “inadequately green” [40].

Conclusion to Chapter II

1. Remdesivir is a complex molecule with six chiral centers and is typically synthesized as a single stereoisomer. It exhibits polymorphism, existing mainly in Form II or its mixtures, both of which demonstrate similar solubility and stability. The substance is practically insoluble in water but highly soluble in organic solvents such as methanol and DMSO, which influences its formulation and analytical strategies.

2. Several synthetic pathways for remdesivir have been developed, with notable contributions from Gilead Sciences. The synthesis involves complex glycosylation, cyanation, and chiral phosphoramidation steps. Despite variations in methods, the final product remains chemically consistent, allowing reliable analytical control.

3. Spectrophotometric methods such as IR- and UV- absorption spectroscopy, along with thin-layer chromatography, are widely employed for remdesivir identification. These methods are effective, relatively simple, and cost-efficient. Each technique confirms the identity of remdesivir through characteristic absorption peaks or chromatographic behavior.

4. Remdesivir can be quantitatively determined using high-performance liquid chromatography, non-aqueous titration, and calorimetric techniques. HPLC remains the gold standard due to its high sensitivity, accuracy, and ability to detect

impurities. Multiple mobile phase systems and column types allow flexibility in method optimization depending on analytical needs.

5. Modern trends in analytical chemistry emphasize the environmental sustainability of techniques. The MoGAPI tool was introduced to evaluate the greenness of remdesivir analytical methods. This tool combines qualitative and quantitative assessments of environmental impact, promoting safer, more sustainable laboratory practices in pharmaceutical analysis.

CHAPTER III
COMPARATIVE EVALUATION OF ANALYTICAL METHODS FOR PHARMACEUTICAL ANALYSIS OF REMDESIVIR IN A SUBSTANCE AND PHARMACEUTICAL PRODUCTS

In the field of pharmaceutical analysis, the accuracy of drug identification plays a pivotal role in ensuring the safety and efficacy of medicinal products. Remdesivir, an antiviral agent used in the treatment of COVID-19, requires highly sensitive and reliable analytical methods due to its complex structure and the necessity of precise dosage control. Among the most widely applied analytical techniques are spectrophotometric and chromatographic methods.

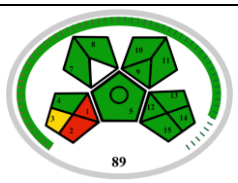
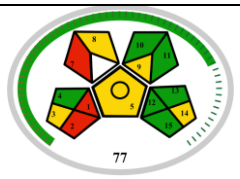
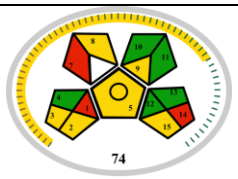
Spectrophotometry offers advantages such as simplicity, rapid analysis, and cost-efficiency, making it suitable for routine quality control, particularly in settings with limited technical resources. On the other hand, chromatographic techniques—especially HPLC—are valued for their superior resolution, selectivity, and ability to identify both the active ingredient and its related impurities within complex formulations.

3.1. Assessment of spectrophotometric and chromatographic approaches for remdesivir identification

In recent decades, many color-based spectrophotometric methods have been developed for the quantitative analysis of pharmaceutical products. Extractive spectrophotometric methods using various acid dyes are commonly used for the determination of many drugs. There are universally different acid dyes, bromothymol blue, bromophenol blue and bromocresol green [41]. Despite the popularity of this method, the selection of the most suitable acid dye requires many experimental trials, as already published in many articles. Moreover, this recommends the consumption of many chemicals, high cost and long analysis time.

Table 3.1

Analytical parameters of spectroscopic and chromatographic methods for remdesivir identification

Parameter	Method of identity		
	IR-spectroscopy (*Section 2.2.1.1)*	UV-spectrophotometry (*Section 2.2.1.2)*	TLC *(Section 2.2.1.3)*
Linearity range (μg)	is not executed	2.0-60.0	0.20 – 4.50
Correlation coefficient (r)	-	0.9998	0.9999
Limit of detection (μg)	1.0	1.418	0.04
Eco-Scale score			

Compared to most other analytical techniques, the spectrophotometric method offers several advantages, including simplicity, cost-effectiveness, and reduced time consumption. Owing to its straightforward and rapid nature, spectrophotometry is a valuable tool in pharmaceutical analysis.

Based on the comparative analysis of IR spectroscopy, UV spectrophotometry and thin-layer chromatography (TLC), it can be concluded that TLC demonstrates the highest sensitivity with the lowest detection limit (0.04 μg), which makes it very effective for identifying corrective methods in this trace, however, as an indicator of environmental friendliness, as well as the analyzed one, it has greenness coefficients at 74, the lowest compared to other methods. UV spectrophotometry demonstrates a wide range of linearity (2.0-60.0 μg) and excellent correlation (r = 0.9998), which indicates that the technique can be used not only for compound identification but also for the multiquantitative determination of the API. Although IR spectroscopy is limited in terms of quantitative determination, it remains a reliable method for confirming structural identity. In general, each method offers advantages, but all of them can be used for

quality control of remedivir pharmaceutical products in different capacities and different laboratory settings.

3.2. Evaluation of HPLC techniques for remdesivir quantification and quality control

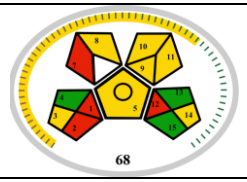
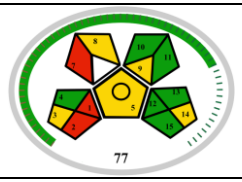
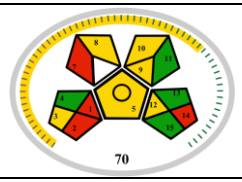
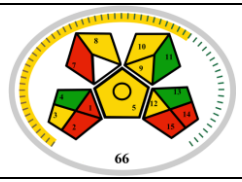
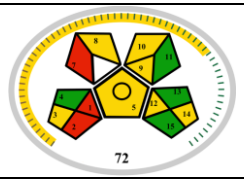
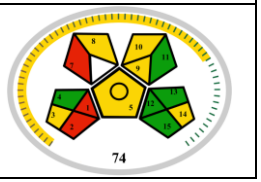
HPLC has established itself as one of the most important methods in the pharmaceutical analysis of APIs, including remdesivir. Despite facing criticism from an economic and environmental standpoint due to the extensive consumption of high-purity organic solvents, labor-intensive sample preparation, and the high cost of equipment acquisition and maintenance, HPLC remains indispensable in modern pharmaceutical sciences. This is largely attributed to its exceptional sensitivity, selectivity, robustness, and versatility, particularly in the analysis of complex biological matrices and drug formulations.

The fundamental principle of HPLC revolves around the separation of components based on their interactions with the stationary and mobile phases. For remdesivir analysis, various mobile phases have been employed, often composed of combinations such as acidified water and acetonitrile or mixtures involving methanol, dimethyl sulfoxide, and buffer solutions. The majority of the methods utilize C18 reversed-phase columns of varying dimensions (150–250 mm in length) and particle sizes (3.5–5.0 μm), operating at flow rates between 0.7 and 1.2 mL/min. Detection is typically carried out using UV-spectrophotometry, with wavelengths ranging from 230 nm to 247 nm to maximize analyte sensitivity.

A comparative overview of different HPLC methods for remdesivir analysis is summarized in the Table 3.2.

Table 3.2

A comparative overview of different HPLC methods for remdesivir analysis

HPLC methods						
Mobile Phase	Ortho-phosphoric acid in water with pH 3.0 (A) and mixture of acetonitrile, methyl alcohol and water (70:20:10) (B) [42]	acetonitrile : water (50:50) [43]	20 mM potassium dihydrogen phosphate solution: acetonitrile (50:50) [44]	Dimethyl sulfoxide: acetonitrile: water (10:60:30) [45]	mixture of 0.025 M Brij-35, 0.1 M sodium lauryl sulfate (SLS), and 0.02 M disodium hydrogen phosphate [46]	water (acidified with phosphoric acid, pH 3) (A) : acetonitrile (50:50) (B) [47]
Column	C18 (250 mm × 4.6 mm, 5 µm)	C18 (150mm x 4.6mm, 3.5 µm)	C18 (150 mm × 4.6 mm, 5 µm)	C18 (150 x 4.6 mm, 3.5 µm)	C18 (150 mm × 4.6 mm, 5 µm)	C18 (150 mm × 4.6 mm, 5 µm)
Flow rate, ml/min	0.7	1	1.2	0.8	1	1
UV detector wavelength	242	230	247	246	244	246
Time of the analysis, min	70	10	10	40	10	10
LOD (µg/ml)	0.121	0.063	3.00	0.74	0.5	0.0195
LOQ (µg/ml)	0.398	0.208	9.00	0.82	2.0	0.0649
Eco-Scale score	 68	 77	 70	 66	 72	 74

Among the reviewed methods (Table 3.2), the technique utilizing an acidified water–acetonitrile mobile phase achieved the highest sensitivity, with a limit of detection of 0.0195 μg/mL. Methods with shorter analysis times (approximately 10 minutes) are preferred for routine quality control applications, as they reduce operational costs and solvent consumption, contributing to greater environmental sustainability.

From an economic perspective, the acquisition and maintenance of HPLC systems represent a substantial investment, especially for smaller clinical laboratories or resource-limited settings. Moreover, the ecological impact associated with the use of large volumes of organic solvents (such as acetonitrile and methanol) necessitates the adoption of green analytical chemistry practices wherever possible.

Based on preliminary assessments, HPLC methods using common organic solvents such as acetonitrile and methanol typically achieve Eco-Scale scores ranging from 60 to 70 points. According to analytical green chemistry standards, these scores classify the methods as " acceptable green " but highlight the need for further improvement to reduce their environmental impact. It should be noted that methods characterized by shorter analysis times, reduced solvent consumption, and optimized mobile phase compositions tend to score higher on the Eco-Scale and exhibit improved MoGAPI profiles, thereby aligning more closely with the principles of green analytical chemistry. This evaluation emphasizes the increasing importance of environmentally sustainable practices in pharmaceutical quality control and method development.

Nonetheless, HPLC remains the method of choice for remdesivir analysis due to its unmatched performance characteristics. It ensures the reliable identification and quantification of the active pharmaceutical ingredient, facilitates impurity profiling, and supports regulatory submissions through validated, internationally recognized methodologies. Additionally, HPLC's ability to adapt to various formulation matrices and its compatibility with advanced detection

systems such as diode array and mass spectrometry significantly broaden its application range in both research and quality control environments.

In conclusion, while it is essential to address the economic and environmental challenges associated with HPLC, its critical role in pharmaceutical analysis, particularly for complex molecules like remdesivir, is unquestionable. Through method optimization and the integration of green chemistry principles, the advantages of HPLC can be maximized, ensuring high-quality analytical performance while minimizing the environmental footprint.

3.3. Comparison of analytical methods based on time, sensitivity, and cost

A comparative analysis of the various analytical methods based on key parameters such as analysis time, sensitivity, operational costs, and environmental impact can provide a more holistic perspective. Spectrophotometric techniques, particularly UV-visible spectrophotometry, offer rapid analysis within 10 to 15 minutes, low detection limits around 1.4 μg/mL, and minimal environmental burden, making them highly suitable for routine use in quality control laboratories. Thin-layer chromatography (TLC), although exhibiting superior sensitivity with a limit of detection as low as 0.04 μg/mL, generally requires longer analysis times and may be less practical for high-throughput environments. HPLC methods, while providing exceptional sensitivity (with detection limits as low as 0.0195 μg/mL) and the ability to separate and quantify impurities effectively, are associated with higher operational costs, more complex sample preparation, and greater environmental concerns due to the use of organic solvents and energy-intensive instrumentation.

Table 3.3.

Comparison of analytical methods for remdesivir determination

Criterion	Methods		
	UV-spectrophotometry	TLC	HPLC
Analysis time	10–15 min	30–40 min	10–70 min (depending on method)
Sensitivity (LOD)	~1.4 μg/ml	~0.04 μg/ml	0.0195–3.00 μg/ml
Operational costs	Low	Very low	High
Environmental impact	Minimal	Minimal	Moderate to high
Suitability for routine quality control	High	Moderate	High (for detailed analysis)

Given these considerations, it is advisable to formulate clear recommendations regarding the selection of analytical methods for different pharmaceutical analysis tasks involving remdesivir. For routine quality control applications where rapid results, simplicity, and cost-efficiency are critical, UV-spectrophotometry represents the most practical and environmentally favorable choice. Its ease of use, minimal sample preparation, and compatibility with standard laboratory equipment make it ideal for frequent testing scenarios. In contrast, for detailed impurity profiling, bioequivalence studies, validation of manufacturing processes, and regulatory submissions, HPLC remains the preferred method due to its unparalleled analytical performance, precision, and robustness.

Conclusion to Chapter III

1. A comprehensive comparative evaluation of analytical methods for the identification and quantification of remdesivir in substances and pharmaceutical products was conducted. Spectrophotometric techniques, including UV- and IR- and also chromatography methods like TLC, were found to offer significant advantages such as simplicity, rapid analysis, and cost-effectiveness. UV-spectrophotometry demonstrated a wide linearity range (2.0–60.0 μg/mL) and excellent correlation (r = 0.9998), making it suitable for routine quality control, whereas TLC showed the highest sensitivity with a LOD of 0.04 μg/mL, although it required more time for analysis.

2. HPLC remains the gold standard for the analysis of remdesivir, offering superior sensitivity (LOD as low as 0.0195 μg/mL), selectivity, and robustness. HPLC methods were characterized by the use of C18 columns, various aqueous-organic mobile phases, and UV detection between 230 and 247 nm. However, economic and environmental challenges, including high operational costs and the use of organic solvents, limit their widespread routine use.

3. Comparative analysis of time, sensitivity, operational costs, and environmental impact confirmed that UV-spectrophotometry is preferable for rapid, routine quality control tasks due to its low cost and minimal environmental burden. HPLC is indispensable for detailed impurity profiling, pharmacokinetic studies, and regulatory submissions, where high precision and accuracy are essential.

4. The choice of analytical method for remdesivir should be guided by the specific analytical task. UV-spectrophotometry is recommended for routine quality control due to its simplicity and eco-friendliness, whereas HPLC is advised for comprehensive quality assessment and regulatory compliance, despite its higher cost and environmental footprint.

CONCLUSION

1. The review of current literature confirmed that remdesivir is a nucleotide analog prodrug that exerts its antiviral activity by inhibiting RNA-dependent RNA polymerase. Its pharmacokinetic profile is characterized by rapid distribution, extensive intracellular activation to its active triphosphate form (GS-443902), and elimination mainly through the kidneys. The synthesis of remdesivir involves complex chemical processes, including glycosylation and phosphoramidation, requiring strict stereochemical control to ensure product quality and efficacy.

2. A variety of modern analytical techniques have been developed for the identification and quality control of remdesivir, including infrared (IR) spectroscopy, ultraviolet-visible (UV-Vis) spectrophotometry, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). These methods vary in sensitivity, specificity, and practicality. HPLC is considered the most reliable technique for detailed analysis, while UV-Vis spectrophotometry offers simplicity and rapid results suitable for routine quality control.

3. The comparative evaluation revealed that spectrophotometric methods are advantageous for their cost-effectiveness, simplicity, and reduced environmental burden, but they are limited by lower specificity and sensitivity. In contrast, chromatographic methods, particularly HPLC, offer superior sensitivity, selectivity, and the ability to detect impurities, albeit at higher operational costs and greater environmental impact due to solvent usage.

4. The analysis demonstrated that HPLC methods provide the lowest limits of detection and quantification, making them ideal for precise impurity profiling and quantitative determinations. UV-Vis spectrophotometry showed excellent linearity and acceptable sensitivity for routine applications. In terms of environmental impact, UV-Vis spectrophotometric methods were more sustainable compared to traditional HPLC methods, which often require large volumes of organic solvents.

5. The application of Eco-Scale and MoGAPI tools indicated that most traditional HPLC methods achieve only acceptable greenness scores, necessitating optimization for improved environmental performance. Spectrophotometric methods scored higher on sustainability metrics due to their minimal use of hazardous chemicals and lower energy consumption, aligning better with the principles of green analytical chemistry.

6. Based on the obtained results, UV-Vis spectrophotometry is recommended for routine quality control of remdesivir because of its rapid analysis time, simplicity, low cost, and eco-friendliness. HPLC methods are strongly recommended for comprehensive quality assessments, detailed impurity profiling, and meeting stringent regulatory requirements, where the highest accuracy and sensitivity are essential.

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Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department pharmaceutical chemistry
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational and professional program Pharmacy

APPROVED
The Head of Department
of pharmaceutical
chemistry

_____
Victoriya GEORGIYANTS
"_03_" ____September___ 2024 year

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Aicha ZAKI

1. Topic of qualification work: «Selection of analytical methods of remdesivir determination in a substance and pharmaceutical products», supervisor of qualification work: Vasyl GRYNENKO, PhD, associate professor,
approved by order of NUPh from "27th" of September 2024 № 237

2. Deadline for submission of qualification work by the applicant for higher education: may 2025.

3. Outgoing data for qualification work: general characteristics, mechanism of action, pharmacological effects and pharmacokinetic parameters of remdesivir, physicochemical properties, methods of preparation and methods of analysis of the active pharmaceutical ingredient in a substance and pharmaceutical products.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): to review the scientific literature on the pharmacological properties, pharmacokinetics, and synthesis of remdesivir; to analyze modern methods used for the identification and quality control of remdesivir; to evaluate the advantages and disadvantages of spectrophotometric and chromatographic methods applied to remdesivir analysis; to perform a comparative analysis of methods based on key parameters such as sensitivity, linearity, detection limits, and environmental impact; to assess the environmental sustainability of analytical methods using MoGAPI tools; to recommend suitable analytical strategies for routine quality control and regulatory compliance of remdesivir-based pharmaceutical products.

5. List of graphic material (with exact indication of the required drawings):
4 figures, 4 tables, 4 schemas.

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Vasyl GRYNENKO, associate professor of higher education institution of the department pharmaceutical chemistry	11/09/2024	11/09/2024
2	Vasyl GRYNENKO, associate professor of higher education institution of the department pharmaceutical chemistry	24/11/2024	24/11/2024
3	Vasyl GRYNENKO, associate professor of higher education institution of the department pharmaceutical chemistry	18/01/2025	18/01/2025

7. Date of issue of the assignment: "_03_" ____September___ 2024 year

CALENDAR PLAN

№	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Study and analysis of reference data on the use of expectorants. Writing 1 chapter.	Sept-Nov 2024	**done**
2	Study, processing and analysis of literature data on the use of remsedivir, methods of its synthesis, analysis and metabolism and physic-chemical properties. Writing 2 chapter.	Dec 2024 - Jan 2024	**done**
3	Selection of modern methods of quality control of remedivir for pharmaceutical analysis tasks.	Jan-Feb 2025	**done**
4	Analyse and characterise the proposed methods in terms of validation characteristics, time of analysis, environmental friendliness and cost. Writing 3 chapter.	March – April 2025	**done**
5	Summing up, preparation for defense	May 2025	**done**

An applicant of higher education _____ Aicha ZAKI

Supervisor of qualification work _____ Vasyl GRYNENKO

ВИТЯГ З НАКАЗУ № 237

По Національному фармацевтичному університету

від 27 вересня 2024 року

Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу Фм20(4,10д) 2024-2025 навчального року, освітньо-професійної програми – Фармація, другого (магістерського) рівня вищої освіти, спеціальності 226 – Фармація, промислова фармація, галузь знань 22 Охорона здоров'я, денна форма здобуття освіти (термін навчання 4 роки 10 місяців), які навчаються за контрактом (мова навчання англійська та українська) згідно з додатком № 1.

Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі фармацевтичної хімії**				
Закі Аіша	Підбір аналітичних методик визначення ремдесивіру в субстанції та готових лікарських засобах	Selection of analytical methods of remdesivir determination in a substance and pharmaceutical products	доц. Гриненко В.В.	проф. Подольський І.М.

Ректор

Вірно. Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«04» травня 2025 р. № 331110419

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Закі Аіша, групи Фм20(4,10д)англ-02, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Підбір аналітичних методик визначення ремдесивіру в субстанції та готових лікарських засобах / Selection of analytical methods of remdesivir determination in a substance and pharmaceutical products», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Aicha ZAKI

on the topic: «Selection of analytical methods of remdesivir determination in a substance and pharmaceutical products»

Relevance of the topic. The topic of the qualification work is timely and relevant, especially in the context of the COVID-19 pandemic, where remdesivir became a crucial antiviral agent. The development and comparative evaluation of analytical methods for remdesivir in substances and pharmaceutical products are important to ensure the quality, efficacy, and safety of antiviral therapies.

Practical value of conclusions, recommendations and their validity. The work presents a comparative analysis of spectrophotometric and chromatographic methods, with particular attention to analytical performance and environmental sustainability. The use of MoGAPI and Eco-Scale tools demonstrates the applicant’s awareness of green analytical chemistry principles. The conclusions are well-founded and supported by experimental data, and they provide practical recommendations for optimizing quality control strategies for remdesivir.

Assessment of work. The qualification work is executed at a high scientific level. The student independently analyzed current scientific literature, evaluated modern analytical techniques, and performed a critical comparison based on sensitivity, detection limits, and ecological impact. The research reflects a solid understanding of pharmaceutical analysis principles and environmental considerations.

General conclusion and recommendations on admission to defend. The qualification work of Aicha ZAKI meets the requirements for master's theses and is recommended for defense before the Examination Commission.

Scientific supervisor _____ Vasyl Grynenko

«12th» of May 2025

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Aicha ZAKI

on the topic: «Selection of analytical methods of remdesivir determination in a substance and pharmaceutical products»

Relevance of the topic. The topic is highly relevant due to the widespread use of remdesivir as a key antiviral agent during the COVID-19 pandemic. The lack of unified standards in international pharmacopoeias for remdesivir determination underscores the necessity for developing modern and validated analytical methods. The comparative study of spectrophotometric and chromatographic methods contributes significantly to ensuring the quality, efficacy, and safety of this vital medicinal product.

Theoretical level of work. The qualification work is executed at a high theoretical level. The author demonstrates a strong grasp of pharmaceutical analysis and green chemistry principles, thoroughly analyzing modern literature, regulatory requirements, and technical approaches. The methodology includes comprehensive theoretical reasoning, substantiating the selected experimental procedures.

Author's suggestions on the research topic. The author proposes a well-founded comparative assessment of analytical methods with emphasis on their ecological and analytical efficiency. While the work contains strong metrological support, a deeper discussion of validation parameters for the preferred methods (HPLC and UV-spectrophotometry) could enhance the practical implications of the proposed recommendations.

Practical value of conclusions, recommendations and their validity. The conclusions are logically structured and supported by solid experimental results and environmental assessment tools (Eco-Scale, MoGAPI). The work offers valuable

recommendations for pharmaceutical companies and quality control laboratories, supporting the integration of sustainable practices into routine analysis.

Disadvantages of work. The work submitted for review does not reveal any substantial shortcomings. Minor improvements could include an expanded discussion of method validation in real-world manufacturing settings.

General conclusion and assessment of the work. The qualification work meets the requirements for master's level theses and can be recommended for defense before the Examination Commission.

Reviewer _____ prof. Ilya PODOLSKY

« 14th » of May 2025

Ф А2.2.1-91-287

ВИТЯГ

з протоколу засідання кафедри фармацевтичної хімії

№ 14 від 16 травня 2025 р.

Засідання проводилось з використанням ZOOM технологій з 12 год. 05 хв. по 12 год. 50 хв.

Чисельний склад кафедри: 16 науково педагогічних працівників, з них присутні – 16 осіб.

ПРИСУТНІ: зав.каф. проф. Георгіянц В.А., професори: Баюрка С.В., Перехода Л.О., Северіна Г.І., Сидоренко Л.В., доценти: Амжад Абу Шарк І., Бевз Н.Ю., Віслоус О.О., Головченко О. С., Гриненко В.В., Кобзар Н.П., Михайленко О.О., Петрушова Л.О., Рахімова М.В., Яременко В.Д., ас. Григорів Г.В.; аспіранти: Асмолов В. Є., Гончар О.О., Гуріна В. О., Коптєлов А. С., Куцанян А. А., Мураль Д. В., Сайфудінова Р. П., Сулейман Р. М., Суржиков І.О.

ПОРЯДОК ДЕННИЙ:

Звіт про стан виконання кваліфікаційної роботи здобувача вищої освіти фармацевтичного факультету Фм20(4,10д)англ-02 групи, спеціальності «226 Фармація, промислова фармація», освітньо-професійної програми «Фармація» Аіші ЗАКІ на тему: «Підбір аналітичних методик визначення ремдесивіру в субстанції та готових лікарських засобах».

СЛУХАЛИ: доповідь здобувачки вищої освіти фармацевтичного факультету Фм20(4,10д)англ-02 групи, спеціальності «226 Фармація, промислова фармація», освітньо-професійної програми «Фармація» Аіші ЗАКІ на тему: «Підбір аналітичних методик визначення ремдесивіру в субстанції та готових лікарських засобах», керівник – доцент закладу вищої освіти кафедри фармацевтичної хімії, к.фарм.н., доц. Василь ГРИНЕНКО.

УХВАЛИЛИ: рекомендувати кваліфікаційну роботу Аіші ЗАКІ до офіційного захисту в Екзаменаційній комісії.

Голова
зав. кафедри, доктор фарм. наук,
професор **Вікторія ГЕОРГІЯНЦ**

Секретар
доцент, канд. фарм. наук **Марина РАХІМОВА**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Аіша Закі до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньо-професійною програмою Фармація
на тему: «Підбір аналітичних методик визначення ремдесивіру в субстанції та готових лікарських засобах»

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Аіша ЗАКІ виконала кваліфікаційну роботу на високому науково-методичному рівні. У процесі роботи вона продемонструвала глибокі теоретичні знання, аналітичні здібності та вміння застосовувати сучасні методи фармацевтичного аналізу. Структура дослідження є логічною, зміст — послідовним і науково обґрунтованим. Висновки чітко сформульовані, відповідають меті роботи та підтверджуються експериментальними результатами. Кваліфікаційна робота Аіші ЗАКІ відповідає вимогам, що висуваються до кваліфікаційних робіт рівня магістра, і може бути рекомендована до захисту в Екзаменаційній комісії.

Керівник кваліфікаційної роботи

_____ Василь ГРИНЕНКО

«12» травня 2025 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Аіша ЗАКІ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
фармацевтичної хімії

_____ Вікторія ГЕОРГІЯНЦ

«16» травня 2025 року

Qualification work was defended

of Examination commission on

« ____ » __June__ 2025 year

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Volodymyr YAKOVENKO /