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In Silico Prediction of Biopharmaceutical Features of Remdesivir: A Serendipitous Drug for COVID-19

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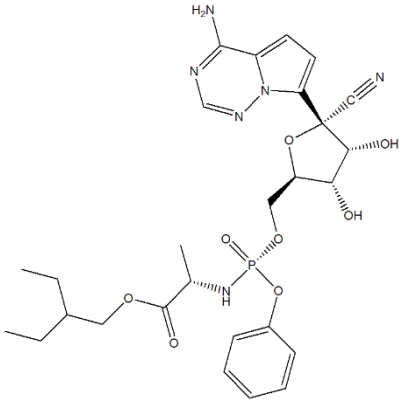
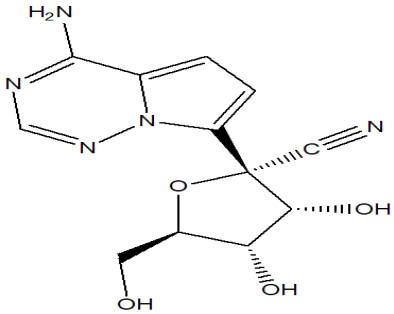
In Silico Prediction of Biopharmaceutical Features of Remdesivir: A Serendipitous Drug for COVID-19: Graphical Abstract

Remdesivir
(GS-5734, inactive prodrug)
administered intravenously



GastroPlus version 9.7

Nucleoside core
(GS-441524)



ADMET Predictor

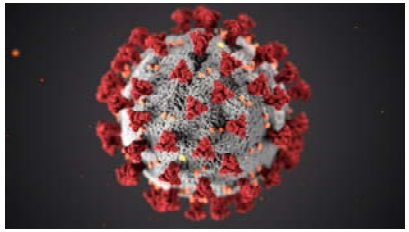
PKPlus modules

Simulation

Abstract: Due to the novel nature of the Coronavirus Disease 2019 (COVID-19), there is limited or no standard treatment for it. Remdesivir is the only approved agent for COVID-19, however, there is limited information available about the physicochemical and pharmacokinetic (PK) properties of this drug. The objective of this in silico simulation work was to simulate the biopharmaceutical behavior of remdesivir. The Spatial Data File format structures of remdesivir prodrug and nucleoside core were obtained from the PubChem database to upload on the GastroPlus software 9.7 version. The Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Predictor and PKPlus modules were used to simulate physicochemical and PK properties, respectively, in healthy and predisposed patients. Remdesivir's nucleoside core (GS-441524) was more hydrophilic than the inactive prodrug (GS-5734) with nucleoside core demonstrating better water solubility. Both had low blood brain barrier penetration while GS-5734 predicted to be 100% metabolized by CYP3A4. The bioavailability (Fa%, F%, Cmax, CmaxLiver) of GS-5734 was higher than GS-441524. In addition, there was limited effect of renal function, liver function, weight, or age on the PK profile of remdesivir. GS-5734 (inactive prodrug) appears to be a superior remdesivir derivative due to its hepatic stability, optimum hydrophilic/lipophilic nature, and disposition properties with limited effect of patient physiological conditions.

Keywords: Remdesivir, COVID-19, ADME, Pharmacokinetics, GastroPlus

Introduction: Coronavirus



- Coronavirus disease of 2019 (COVID-19) is caused by the novel beta coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Single-stranded, glycoprotein enveloped, positive-sense RNA viruses
- It consists of four subgroups (alpha, beta, gamma, delta)
- There are a total of seven coronaviruses that can infect humans
  - Alpha viruses: 229E, and NL63
  - Beta viruses: OC43, HKU1, MERS-CoV, SARS-CoV, and **SARS-CoV-2**

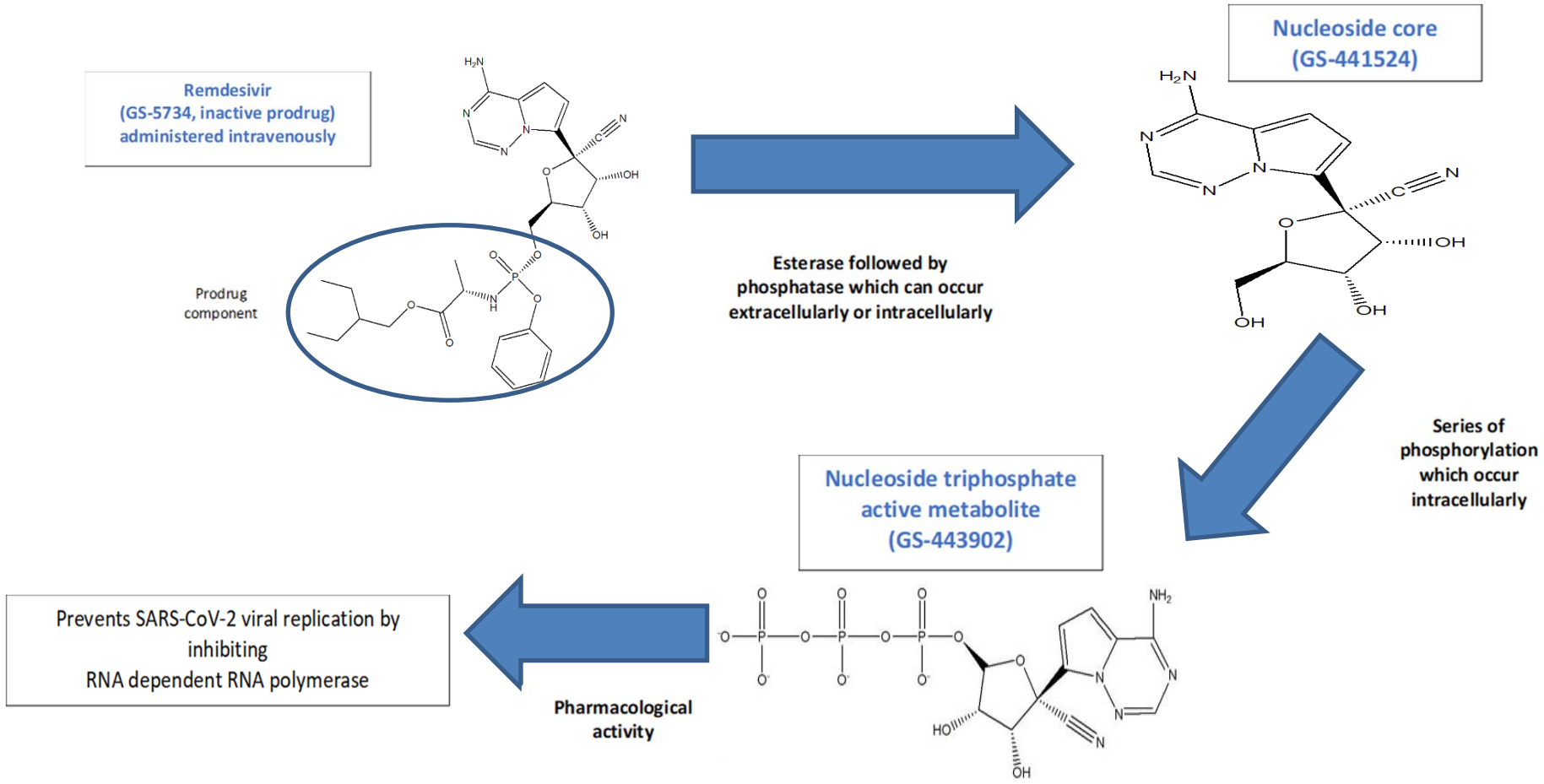
Coronavirus. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/types.html. Published February 15, 2020. Accessed October 29, 2020.
SARS-CoV-2 image: Eckert, Alissa. "SARS-CoV-2." CDC: Public Health Image Library (PHIL), 2020, phil.cdc.gov/Details.aspx?pid=23312.

Introduction: Remdesivir Treatment of COVID-19

- On October 22, 2020 the FDA made remdesivir as the only approved drug against COVID-19.
- Remdesivir was originally developed against Ebola virus but has shown to be somewhat effective against COVID-19.
- Although FDA has approved remdesivir for COVID-19, there is limited information available about its physicochemical and pharmacokinetic (PK) properties.
- The objective of this *in silico* simulation work was to predict the biopharmaceutical properties of remdesivir.

Commissioner, Office of the. FDA Approves First Treatment for COVID-19, 22 Oct. 2020, www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19.

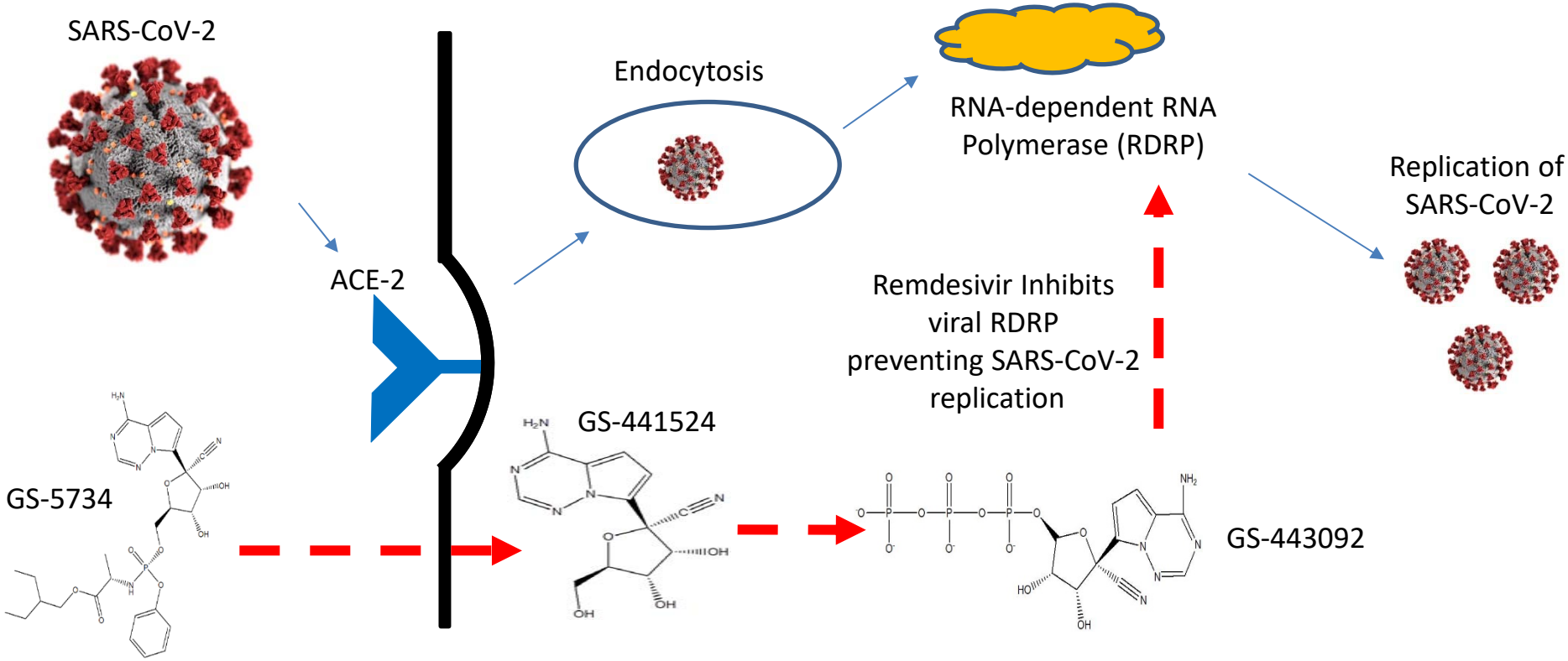
Introduction: Remdesivir Metabolism Pathway



Amirian ES, Levy JK. Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. One Health. 2020;9:100128.
Kim S, Chen J, Cheng T, et al. PubChem 2019 update: improved access to chemical data. Nucleic Acids Res. 2019;47(D1):D1102–D1109.

Introduction: Remdesivir Pharmacological Target

Remdesivir is an adenosine analog prodrug that converts metabolically to GS-441524. GS-441524 is then up taken by infected SARS-CoV-2 lung cells. Intracellularly GS-441524 becomes GS-443902 a nucleoside triphosphate metabolite after a series of phosphorylations. The active nucleoside triphosphate selectively inhibits its **pharmacological target viral RNA-dependent RNA polymerase,** preventing replication of SARS-CoV-2.



Yan VC, Muller FL. Advantages of the Parent Nucleoside GS-441524 over Remdesivir for Covid-19 Treatment. ACS Med Chem Lett. 2020;11(7):1361-1366.
SARS-CoV-2 image: Eckert, Alissa. "SARS-CoV-2." CDC: Public Health Image Library (PHIL), 2020, phil.cdc.gov/Details.aspx?pid=23312.

Methods

- The Spatial Data File format structures of remdesivir prodrug and nucleoside core were obtained from the PubChem database to upload on the GastroPlus software 9.7 version.

- The Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Predictor and PKPlus modules were used to simulate physicochemical and PK properties, respectively, in healthy and predisposed patients.

- **PK models simulated include:**
  - Compartmental
  - Age 30, 70 kg, healthy
  - Age 30, 70 kg, moderate kidney impairment
  - Age 30, 70 kg, Child-Pugh score B
  - Age 30, 85.53 kg, BMI 32 Obese
  - Age 40, 87.58 kg, BMI 28 Overweight
  - Age 75, 70 kg, healthy

Results and Discussion

Table 1. Preliminary estimation of physicochemical properties of remdesivir using GastroPlus software.

Compound	log P	MW (g/mol)	Solubility (µg/mL)	Diff. Coeff (cm^2/s x 10^{-5})	P_{eff} (cm/s x 10^{-4})	pKa Microstates
GS-5734, inactive prodrug	1.6	602.59	0.023	0.51	0.0841	Acid: 10.93 Base: 3.68
GS-441524, nucleoside core	-1.09	291.27	2.6	0.84	0.3	Base: 3.76

Results and discussion

Table 2. Preliminary CYP-mediated predicted metabolism and ability to cross blood brain barrier (BBB) of remdesivir determined by ADMET Predictor feature of the GastroPlus software.

Compound	BBB penetration	Predicated CYP fm	Mechanism of Clearance
GS-5734, inactive prodrug	Low	3A4 = 100%	Metabolism
GS-441524, nucleoside core	Low	N/A	Renal excretion

Table 3. Preliminary predicted pharmacokinetic properties using compartmental PK models.

Compound	Dose (mg)	CL (L/h)	$T_{1/2}$ (h)
GS-5734, inactive prodrug	200	48.81	1.18
GS-441524, nucleoside core	400	N/A	N/A

Results and discussion

Figure 1. Preliminary plasma concentration of 1-hour IV infusion of 200 mg remdesivir (GS-5734, inactive prodrug).

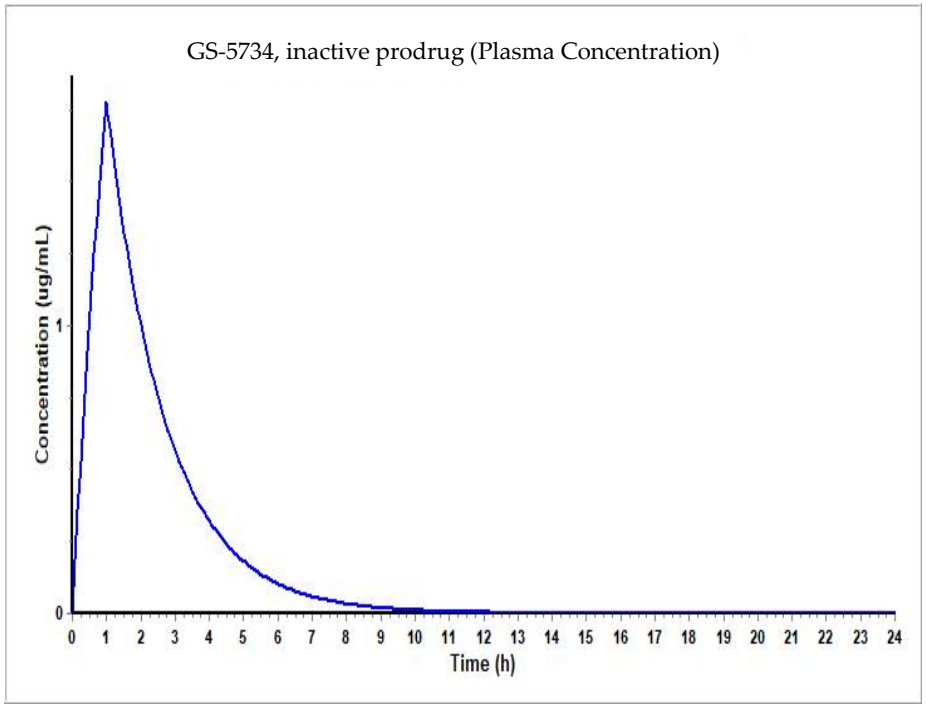
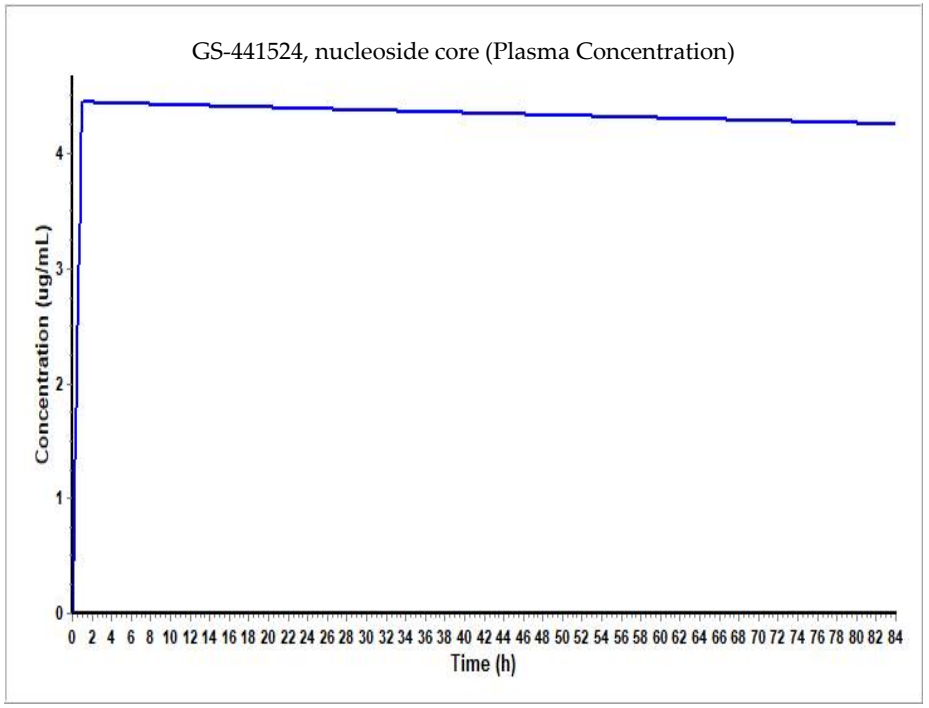


Figure 2. Preliminary plasma concentration of 1-hour IV infusion of 100 mg remdesivir (GS-441524, nucleoside core).



Results and Discussion

Table 4. Preliminary predicted pharmacokinetic parameters of 1-hour IV infusion of 200 mg remdesivir (GS-5734, inactive prodrug) in different simulated populations. The PKPlus platform was used in a single compartment model.

Simulated populations (male)	Fa%	F%	C_{max} (µg/mL)	$C_{max\ Liver}$ (µg/mL)	T_{max} (hr)(sim)	$AUC_{0-\infty}$ (µg - h/mL)	AUC_{0-24} (µg-h/mL)
Age 30, 70 kg, healthy	99.67	99.50	9.46	3.95	1	5.74E+4	179.58
Age 30, 70 kg, moderate kidney impairment	99.63	99.45	9.49	3.97	1	5.23E+4	181.38
Age 30, 70 kg, Child-Pugh score B	99.56	99.34	8.77	3.68	1	4.32E+4	178.52
Age 30, 85.53 kg, BMI 32 Obese	99.70	99.55	7.95	3.32	1	5.24E+4	147.82
Age 40, 87.58 kg, BMI 28 Overweight	99.70	99.55	7.75	3.24	1	5.22E+4	145.16
Age 75, 70 kg, healthy	99.67	99.50	9.74	4.05	1	5.72E+4	181.76

Results and discussion

Table 5. Preliminary predicted pharmacokinetic parameters of 1-hour IV infusion of 100 mg of GS-441524 (nucleoside core) in different simulated populations. The PKPlus platform was used in a single compartment model.

Simulated populations (male)	Fa%	F%	C_{max} (µg/mL)	C_{max} Liver (µg/mL)	T_{max} (hr)(sim)	AUC $_{0-\infty}$ (µg - h/mL)	AUC $_{0-24}$ (µg-h/mL)
Age 30, 70 kg, healthy	87.90	87.06	4.03	2.30	1	2175.10	263.72
Age 30, 70 kg, moderate kidney impairment	87.70	86.85	3.98	2.27	1	2108.70	259.83
Age 30, 70 kg, Child-Pugh score B	87.04	86.15	3.80	2.18	1	1995.50	259.02
Age 30, 85.53 kg, BMI 32 Obese	88.12	87.29	3.60	2.05	1	1977.80	235.25
Age 40, 87.58 kg, BMI 28 Overweight	88.39	87.57	3.40	1.94	1	1977.80	222.39
Age 75, 70 kg, healthy	87.88	87.04	4.06	2.30	1	2175.10	264.07

Conclusions

- GastroPlus software was useful in predicting physicochemical and pharmacokinetic properties remdesivir and its derivatives.
- GS-5734, inactive prodrug was more lipophilic, and expressed a clearance via metabolism.
- GS-441524, nucleoside core was more hydrophilic being eliminated via excretion.
- GS-5734 (inactive prodrug) appears to be a superior remdesivir derivative due to its hepatic stability, optimum hydrophilic/lipophilic nature, and disposition properties with limited effect of patient physiological conditions.
- Potential applications will require additional validation using further *in vitro* and *in vivo* studies.

Acknowledgments

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SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

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College of Pharmacy

For additional information and potential collaboration, please contact ***Dr. Subrata Deb*** *at* *sdeb@alumni.ubc.ca* / *sdeb@ularkin.org*