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Analytical Profile of Antiviral Drugs-Remdesivir, Simeprevir, and Sofosbuvir: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Remdesivir (RDV) is an antiviral drug and a phosphonamidite prodrug designed to have activity against a broad spectrum of viruses, act as a nucleoside analogue, and inhibit the RNA-dependent RNA polymerase [RDRP] of coronaviruses, including SARS-CoV-2, whereas Simeprevir (SMV) and Sofosbuvir (SFS) are direct-acting antiviral drugs approved for the treatment of chronic Hepatitis C virus (HCV) infection. Reports show that the structure and replication mechanism of HCV and SARS-COV-2 are comparable. Hepatitis C virus protease inhibitors include Simeprevir. Because it is an NS3/4A protease inhibitor, it inhibits protein synthesis, which stops viruses from maturing. A nucleotide analogue inhibitor called sofosbuvir selectively blocks the RNA-dependent RNA

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polymerase of HCV NS5B (non-structural protein 5B). This review article gathers and discusses the range of analytical techniques—UV, HPLC, and hyphenated procedures like LC-MS—that are available in the literature for the determination of RDV, SMV, and SFS. This review article can be effectively explored to conduct future analytical investigation for the estimation of the selected drugs in pharmaceutical and biological samples.

Keywords: Remdesivir; Simeprevir; Sofosbuvir; SARS COV-2; HCV; UV; HPLC; LC-MS.

1. INTRODUCTION

"Scientists are exploring various antiviral medications to combat COVID-19, the illness triggered by the novel coronavirus (SARS-CoV-2). They function by inhibiting enzymes that activate envelope glycoproteins involved in the virus's entry into cells. Remdesivir (RMV) is unique because it targets the viral RNA-dependent RNA polymerase (RdRp), which is an important part of how viruses copy themselves" [1]. "Additionally, Simeprevir functions as a direct-acting antiviral agent by inhibiting the HCV NS3/4A protease. Originally used to treat chronic hepatitis C virus (HCV) infections in adults with specific HCV genotypes" [2]. "Similarly, sofosbuvir is another direct-acting antiviral agent employed in combination with other antiviral medications to treat certain hepatitis C virus (HCV) infections" [3].

The main Purpose of this review is to put together a comprehensive list of analytical methods for RDV, SMV, and SFS, thoroughly examining and presenting information on various techniques reported in literature for determining these substances in bulk, pharmaceutical formulations, and diverse biological matrices such as blood plasma, serum, and urine. The analytical methodologies encompass a spectrum of approaches including spectroscopic, chromatographic, and hyphenated techniques, utilized for the quantification of these selected analytes in both bulk quantities, pharmaceutical dosage forms, and biological samples. Fig. 1 depicts the chemical structures, while Table 1 outlines a listing of available marketed formulations for RDV, SMV, and SFS.

2. MECHANISM OF ACTION OF REMDESIVIR

Remdesivir (RMV) works by specifically impeding the activity of the viral RNA-dependent RNA-polymerase (RdRp), a crucial factor in viral replication. Once inside the cell, Remdesivir undergoes rapid metabolism, transforming into a nucleoside monophosphate known as GS-441542 MP. which functions as an adenosine triphosphate (ATP) analog. As a result, GS-441524 can be utilized as a substrate by the viral RdRp. Its incorporation into the newly synthesized RNA strand outcompetes ATP, leading to premature termination of the RNA product. However, unlike conventional chain-terminating agents, the introduction of GS-441524 causes delayed chain termination downstream from this point. Notably, GS-441524 has the ability to evade proofreading by the viral exoribonuclease (ExoN) [4,5]. The detailed mechanism of action of RDV is illustrated in Fig. 2.

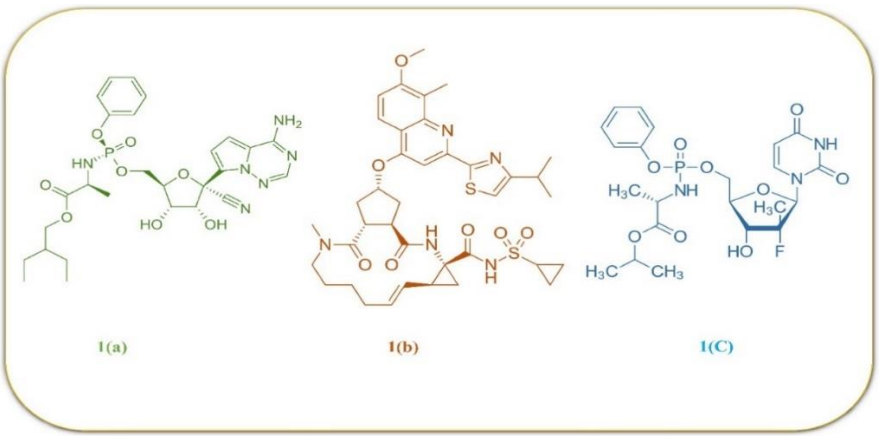

Fig. 1. Chemical structures of (a) Remdesivir; (b) Simeprevir; (c) Sofosbuvir

Table 1. List of some marketed formulations of Remdesivir, Simeprevir and Sofosbuvir

Drug	Trade Name	Name of the manufacturer	Dosage form and strength
Remdesivir	Cipremi	Cipla	Lyophilised Powder for Injection,100 mg
	Redyx	Dr Reddy's	Lyophilised Powder for Injection, 100 mg
	Covifor	Hetero Drugs	Lyophilised Powder for Injection, 100 mg/vial
	Desrem	Mylan	Lyophilised Powder for Injection, 100 mg/vial
	Jubi-R	Jubilant Pharma	Lyophilised Powder for Injection, 100 mg/vial
	Remidac	Zydus Cadila	Injection, 100 mg/vial
	Veklury	Gilead	Injection, 100 mg/ mg/vial
Simeprevir	Olysio	Janssen Pharmaceuticals, Inc.	Capsule, 150 mg
Sofosbuvir	Sovaldi	Gilead Sciences, Inc.,	Tablets, Pellets 400 mg
	Hepcinat	Natco	Tablet, 400 mg
	Myhep	Mylan	Tablet, 400 mg
	Sovihep	Zydusheptiza	Tablet, 400 mg
	Sofovir	Hetero Drugs	Tablet, 400 mg
	Solocure	Emcure	Tablet, 400 mg
	Viroclear	Abbott	Tablet, 400 mg

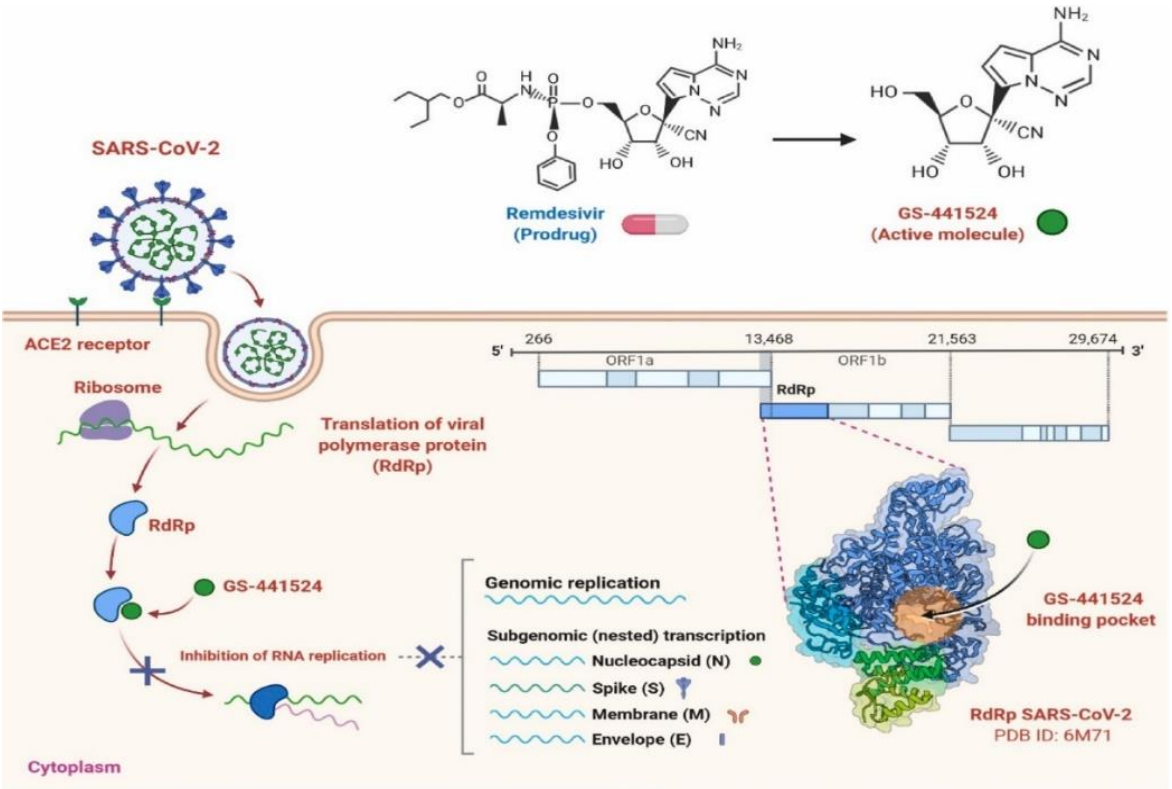

Fig. 2. Mechanism of action of Remdesivir

3. MECHANISM OF ACTION OF SIMEPREVIR

"Simeprevir primarily accumulates in the liver with entering hepatocytes through OATP1B1/3. The NS3/4A heterodimeric complex is made up of two parts: the N4A cofactor subunit and the N3 subunit, which has the proteolytic site. This NS3/4A protease cuts the HCV polyprotein just below the NS3 site. It then makes important viral non-structural proteins like NS3, NS4A, NS4B, NS5A, and NS5B, which eventually lead to the formation of mature proteins. Simeprevir works by inhibiting HCV polyprotein cleavage and binding to an extended S2 subsite within the NS3 catalytic site. Fit induces this binding, which

impacts the enzymatic action" [5]. "NS3/4A inhibitors typically rely on a few interactions within the substrate binding groove of the viral serine protease. Consequently, they can be susceptible to resistance and treatment failure due to critical mutations in these sites. At concentrations higher than their 50% antiviral activity, Simeprevir and other NS3/4A inhibitors not only stop HCV but also fix IFN signalling pathways that were damaged by NS3/4A protease. This restoration helps to recover innate immune processes. The NS3/4A protease cleaves two crucial adaptor proteins that initiate signalling for the activation of IFN regulatory factor 3 and IFN-α/β synthesis, mitochondrial antiviral-signalling proteins (MAVS, also known as IPS-1, VISA, or Cardiff) and toll/interleukin-1 receptor (TIR)-domain-containing adaptor-inducing IFN-β (TRIF). Inhibiting these adaptor proteins results in impaired interferon induction. NS3/4A inhibitors reverse this blockade, restoring proper IFN-signalling pathways" [6-9].

4. MECHANISM OF ACTION OF SOFOSBUVIR

"Sofosbuvir works as a nucleotide analogue inhibitor, focusing on the HCV NS5B (non-structural protein 5B) RNA-dependent RNA polymerase. It undergoes intracellular processing to become the pharmacologically active uridine analogue triphosphate known as GS-461203. This chemical joins with the HCV RNA using the NS5B polymerase and stops the synthesis of the RNA chain" [2]. "To be more specific, sofosbuvir stops the replication of the HCV virus by attaching to two Mg^{2+} ions in the GDD active site motif of the HCV NS5B polymerase. This binding effectively hinders the continuation of HCV genetic material replication" [10-12].

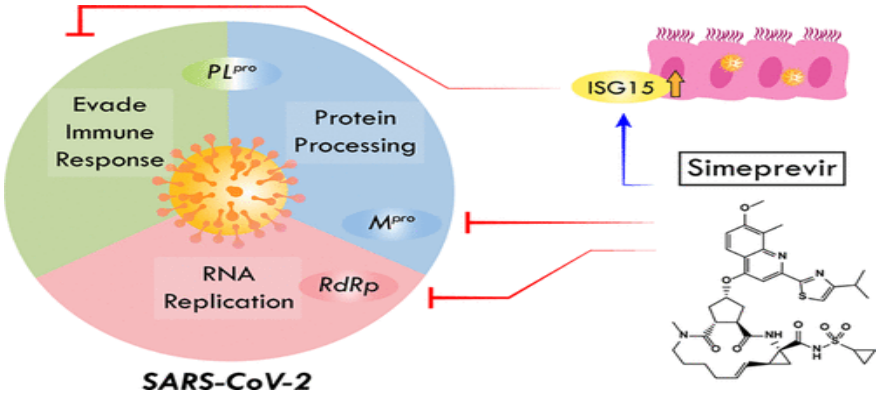

Fig. 3. Mechanism of action of Simeprevir

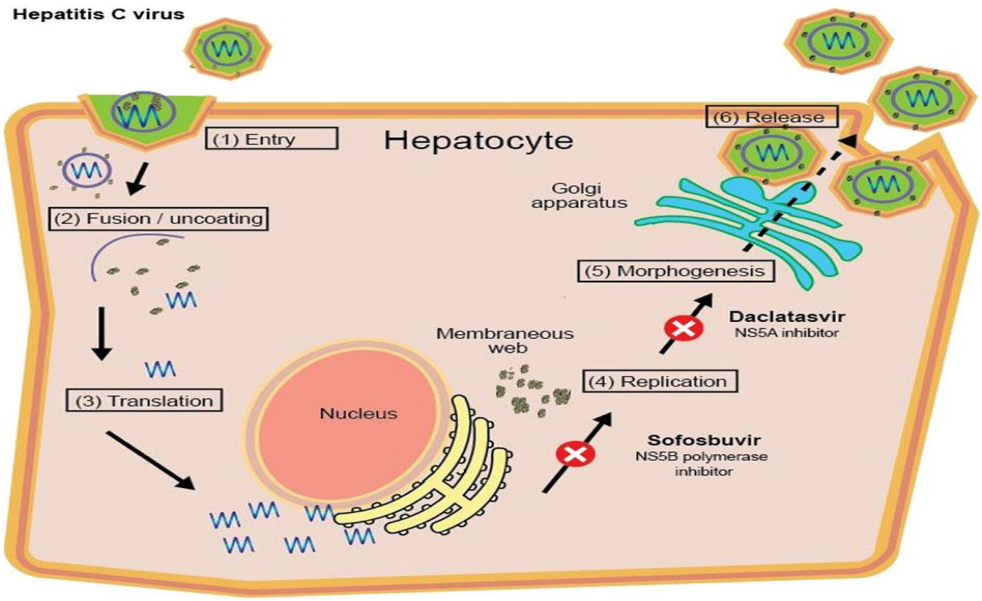

Fig. 4. Mechanism of action of Sofosbuvir

5. ANALYTICAL METHODS

5.1 UV Spectrophotometric Methods

UV Spectrophotometric methods are utilized in the assessment of multicomponent samples, streamlining the labour-intensive process of separating interferons. This approach allows the determination of an expanding array of analytes, effectively reducing both analysis costs and duration. Ultraviolet spectroscopy has been a pivotal and innovative diagnostic tool within the pharmaceutical industry for over three decades. Operating within the near UV region of the spectrum (200-400 nm), this technique measures monochromatic light absorption by colorless substances. Its application extends to discerning the nature, characteristics, quality, and integrity of such substances. Analysts leverage various UV Spectrophotometric techniques to swiftly analyze multicomponent formulations, biotherapeutic products, and intricate matrices. Within this realm, scientists have documented diverse UV spectroscopic methods for estimating RDV, SMV, and SFS, as detailed in Table 2 [11-20].

Table 2. Different UV analytical methods for the estimation of Remdesivir Simeprevir, and Sofosbuvir

Drug	Formulation	Instrument	Solvent	Wavelength (nm)	Linearity (µg/mL)	LOD (µg/mL)	LOQ (µg/mL)	Ref No
Remdesivir	Powder and Injection	Shimadzu UV–Visible Spectrophotometer (1650)	Ethanol	418	2–12	-	-	11
	Injection	Shimadzu UV-1800 Spectrophotometer	Methanol Ethanol Isopropyl alcohol	247	10-60	3.0	9.0	12
Simeprevir	Powder	Shimadzu UV–Visible 1800 Spectrophotometer	DMSO Ethanol	333	3-45	0.888	2.692	13
	Powder	JASCO model FP-6300 spectrofluorometer	Ethanol	290 428	0.05–1.0	0.016	0.048	14
	Powder	JASCO model FP-6300 spectrofluorometer	Ethyl alcohol	429	60–1500	9 ng/ mL	27 ng/ mL	15
	Capsules Powder	JASCO FP-6200 spectrofluorometer (Japan),	Ethanol	442	0.2–2.0	0.0425	0.1288	16
Sofosbuvir	Tablets	Shimadzu UV–Visible Spectrophotometer (1650)	Methanol	244.8	4–40	-	-	17
	Tablets	UV - Visible double beam Spectrophotometer (UV 1800S)	Methanol	261	5.0 - 30	1.51	5.0	18
	powder	ELICO SL 210 Double Beam UV-visible spectrophotometer	Ethanol	261	2-10	0.23	0.70	19
	Tablets	Shimadzu Double beam UV/visible Spectrophotometers model (1601)	Chloroform and Methanol	260	5 - 100	1.6	4.8	20

Table 3. HPLC analytical methods for the estimation of Remdesivir Simeprevir, and Sofosbuvir

Drug and Method	Formulation	Column	Mobile Phase	Detection Wavelength (nm)	Flowrate (mL/min)	Linearity (µg/mL)	LOD (µg/mL)	LOQ (µg/mL)	Ref No.
Remdesivir RP-HPLC	Tablet	Zorbax SB C_{18} Column	Acetonitrile: Water 50:50 (v/v)	230	1	10-150	0.063	0.208	21
	Powder	RP-C18	A mixture of 0.025M Brij-35, 0.1M sodium lauryl sulphate (SLS), and 0.02M disodium hydrogen phosphate, (pH 6.0)	244	1	5-100	0.5	2.0	22
	Injection and Powder	C-18 column	20 mM KH_2PO_4 solution and acetonitrile (50:50, v/v)	247	1.2	10–60	2.40	7.30	23
	Injection	C18 column	Acetonitrile and distilled water (acidified with phosphoric acid, pH 4) 55:45 v/v	240	1	0.1–15	0.10	0.03	24
Simeprevir RP-HPLC	Powder	Discovery C18	Orthophosphoric acid (OPA) and acetonitrile (ACN)55:45% v/v	300	1	25–150	25–150	2.90	25
	Capsules	Discovery HS C18	Acetonitrile	288	1	1.5 - 45	0.4304	1.3044	26
	Solution	XTerra RP18 (150 mm × 4.6 mm, 3.5 µm)	Phosphate buffer (pH 6, 52.5 mM) and Acetonitrile (30:70, v/v)	225	1.0	0.05–20.0	0.02	0.05	27
	Tablets	Inertsil ODS 150 mm x 4.6 mm;5µm	TFA- Buffer (pH -2.0), Acetonitrile: Methanol (30:50:20% v/v/v)	267	1.0	40-120	0.015	0.05	28
Sofosbuvir RP-HPLC	Tablets	Kromasil C18 (250 mm×4.6 mm, 5µm)	Buffer: Acetonitrile taken in the ratio 45:55 %v/v	260	1.0	100-600	0.15	0.46	29
	Tablets	Luna C8, 250 × 4.6 mm, 5 µm,	Ammonium acetate buffer solution pH 7.0 and acetonitrile 35:65 % v/v	245	0.7	16-80	0.485	1.619	30
	Tablets	Hypersil TM ODS C18 column (150×4.6 mm, 5 µm)	Methanol: acetonitrile (90:10 %v/v)	260	1	2-60	0.25	1.70	31

Table 4. Different LC-MS analytical methods for the estimation of Remdesivir Simeprevir, and Sofosbuvir

Drug And Method	Formulation	LC Instrument and Column	Chromatographic conditions	MS-Conditions	Ref No.
Remdesivir LC-MS	Injection	Perkin Elmer LX-50 UHPLC system coupled with a Triple Quadrupole Q Sight 220 Acquity HSS T3 1.8 µm, 2.1% 50 mm column	Mobile phase A: water and formic acid (0.05%) Mobile phase B: ACN and formic acid (0.05%) Run time: 4 min; Flow rate: 0.4 mL/min Injection volume: 8 µL; Retention time: 1.67 min	Positive electrospray ionization Drying gas temp: 130°C HSID temp: 270°C Source temp: 350°C Collision pressure: 410 psig LOD: 0.24 ng/mL; LOQ: 0.98 ng/mL	32
	Injection	Waters, Milford, MA) Acquity UPLC HSS T3 column (2.1×50 mm, 1.8 µm	Mobile Phase A: 10 mM ammonium formate in 5% methanol, pH 2.5 Mobile Phase B: 100% methanol Flow rate: 0.5 ml/min Run time: 3.4 min	API – 5000 triple quadrupole mass-spectrometer, equipped with Turbo Ion spray MS/MS detection Temp: 650˚C Ion spray voltage: 4500 V Entrance potential: 10 V Scan duration: 2.5 min Linearity: 4–4000 ng/mL; LOQ: 4 ng/mL	33
	Injection	UHPLC-1290 infinity II (Agilent Technologies, Germany) Accucore C_{18} (4.6 x 150 mm, 2.6 mm) column	Mobile phase A: 0.1% formic acid in water Mobile phase B: Acetonitrile Flow rate: 0.5 mL/min Retention time: 12.55 min Injection volume: 1 µL	6545 Q-TOF (Agilent Technologies, Germany) UHPLC was directed into the mass spectrometer through an electro-spray ionization mode. Gas temp: 325°C; Gas flow rate: 12 L/min N_2 gas temp: 275°C; N_2 gas flow: 12 L/min Nozzle voltage: 1000 V Nebulizer gas pressure: 30 psig Fragmentor: 80 V; Skimmer: 60 V Mass spectra range: 50-1700 m/z	34
	Injection	Dionex Ultimate 3000 pump using Kinetex 2.6 µm Polar C18 100A LC column (100 × 2.1 mm i.d.) preheated at 30 °C	Mobile phase A: 10 mM sodium formate buffer in 0.1% formic acid Mobile phase B: Acetonitrile Run time: 5 min	TSQ Endura triple quadrupole MS equipped with an ESI set in a positive mode Ion spray potential: +3.5 KV Capillary temp: 350°C N_2 gas: 35 arbitrary pressures	35

Drug And Method	Formulation	LC Instrument and Column	Chromatographic conditions	MS-Conditions	Ref No.
			Flow rate: 0.5 mL/min	Argon gas pressure:1.5 m Torr Linearity: 1–5000 µg/mL LOD: 0.3 µg/mL; LOQ; 1 µg/mL	
	Injection	LC-20ADXR system (Shimadzu, Japan) Waters X Bridge C18 column (50 × 2.1 mm, 3.5 µm)	HPLC-grade methanol (MeOH), acetonitrile (ACN), and isopropanol (IPA) were utilized for preparing stock or working solutions and mobile phases.	QTRAP 5500 spectrometry Set at 55°C. Linearity: 2–1000 µg/mL LOQ: 5 pg/mL	36
Simeprevir LC-MS	Injection	Acquity UPLC	Column: BEH C18 Column, (2.1 mm × 50 mm,1.7 µm Waters, Milan, Italy) maintained at 50°C through the column oven. Mobile phase A: Ammonium acetate 5 mM buffer, pH 9.5) Mobile phase B ACN) at flow rate of 0.4 mL/min and a time run of 5 min.	Tandem mass spectrometer ESI. Capillary voltage: 4KV, Nebulizing gas flow: 3 L/min, Drying gas flow:10 L/min, Heating gas flow: 10 L/min, Interface temperature: 300˚C, Heating block temp: 400˚C, Desolvation line temp: 250˚C. Linearity: 2000 ng/mL LOD: 1.2 ng/mL; LOQ: 4.9 ng/mL	37
	Injection		Mass Tox® TDM Series Column A (50 × 2 mm) C18 column Mobile phase A: Water + formic acid 0.1%) Mobile phase B: Methanol + formic acid 0.1%)	AB Sciex Qtrap 5500 mass spectrometer with an ESI+ Collision gas: medium, Curtain Gas: 30 units, Ion spray voltage: 3000 V, Probe temperature: 550 °C, Dwell time: 50 ms. Linearity: 15.6- 2000 ng/mL LOD: 1.2 ng/mL: LOQ: 15.6 ng/mL	38
Sofosbuvir LC-MS	Injection	Waters Acquity H class UPLC	Acquity H class UPLC BEH C_{18} (1.7 µm 2.1x50 mm) column Mobile phase A: 10mM ammonium formate with 0.05% formic acid in water Mobile phase B: 10mM ammonium formate with 0.05% formic acid in methanol Mobile phase C: 10mM ammonium formate with 0.05% formic acid in	XEVO TQ- S micro-MS/MS With ESI Positive Source temp: 150°C Desolvation temp: 500°C Desolvation gas flow: 950 L/Hr Capillary voltage: 1.2 KV Linearity: 5-2500 µg/L LOD: ng/mL LOQ: ng/mL	39

Drug And Method	Formulation	LC Instrument and Column	Chromatographic conditions	MS-Conditions	Ref No.
			methanol: acetonitrile (10:90) Retention time: 3.32 min Flow rate: 0.4 mL/min Column temperature: 40°C		
	Injection	Acquity H class UPLC BEH C_{18} (1.7 µm 2.1x50 mm) analytical column	Acquity BEH C_{18} (1.7 µm 2.1x50 mm) analytical column	XEVO TQD LC-MS/MS equipped with positive electrospray ionization mode Source temp: 120°C Capillary voltage: 3.0 KV Desolvation gas flow: 800 L/h Desolvation temp: 350°C	40
	Injection	Waters Acquity UPLC H class Acquity H class UPLC C_{18} (50x4.6 mm 5 µm) column	Mobile phase: Methanol: 0.5% formic acid (70:30 v/v) Flow rate:0.5 mL/min Column temp: 40°C	XEVO TQD equipped to positive electrospray ionization mode Source temp: 100°c Capillary voltage: 3.0 KV Desolvation gas flow:600 L/h Desolvation temp: 450°C Linearity: 4.063- 8000 ng/mL	41
	Injection	Agilent 1200 series HPLC-DAD C_{18} (250x4mm i.d., 5 µm)	C_{18} (250x4mm i.d., 5 µm) Mobile phase: water (containing formic acid 0.5 mL/L): acetonitrile (57:43 v/v) Flow rate:0.8 mL/min Column temp: 40°C	Agilent 6410 triple quadrupole mass spectrometer with negative electrospray ionization mode Source temp: 100°C Capillary voltage: 4000 V Nebulizer pressure:40 psi Fragmentor voltage: 10 V Linearity: 25-3200 ng/mL MS: 2.5	42
	Injection	Acquity H class UPLC BEH C_{18} (1.7 µm 2.1x50 mm) column	Mobile phase: Acetonitrile: 0.1% formic acid (50:50 v/v) Flow rate:0.35 mL/min Retention time: 0.52-0.57 min Column temp: 35°C Injection volume: 10 µL	Waters Acquity H class coupled with XEVO TQD system equipped to positive electrospray ionization mode Source temp: 120°C Capillary voltage: 3.5 KV Desolvation gas flow: 800 L/h Desolvation temp: 350°C Linearity: 0.25-3500 ng/mL LOD: 0.5 ng/mL; LOQ: 0.25 ng/mL	43
		Acquity H class UPLC BEH C_{18}	Mobile phase A: acetonitrile	Waters Acquity H class coupled with XEVO	44

Drug And Method	Formulation	LC Instrument and Column	Chromatographic conditions	MS-Conditions	Ref No.
	Injection	(1.7 µm 2.1x50 mm) analytical column	Mobile phase B: 0.1% formic acid in water, Flow rate: 0.4 mL/min Run time: 3 min	TQD triple quadrupole mass spectrometer equipped to positive electrospray ionization mode Source voltage: 50 V Capillary voltage: 3.5 KV Desolvation gas flow:600 L/h Desolvation temp: 500°C Linearity: 10-2000 ng/mL LOQ: 10 ng/mL	
	Tablets	Inertsil ODS-3 reverse phase C_{18} (250mmx4.6mm i.d., 5µm) analytical column	Mobile phase: methanol: water (70:30 v/v) Flow rate:1.3 mL/min Retention time: 4.5 min	Agilent technologies 6420 triple quadrupole LC-MS/MS with positive electrospray ionization mode Linearity: 10-150 µg/mL LOQ: Linearity: 10-2000 µg/mL LOD: 0.1 µg/mL; LOQ: 1 µg/mL	45

5.2 High-Performance Liquid- Chromatography (HPLC) Methods

High-performance liquid chromatography (HPLC), also referred to as high-pressure liquid chromatography, stands as a specific variant of column chromatography employed in biochemistry and analysis. Its purpose lies in the separation, identification, and quantification of active compounds. As one of the most precise analytical techniques extensively utilized for both quantitative and qualitative analyses of drug products, HPLC holds a prominent position in analytical chemistry. The separation process hinges on the interaction between the mobile phase and stationary phase, the fundamental elements of HPLC, possessing contrasting polarities and equipped with high-pressure pumps. Different HPLC methods have been documented for the quantification of RDV, SMV, and SFS, are shown in Table 3 [21-31]. These methods offer varied approaches to determine these compounds accurately.

5.3 Liquid Chromatography-Mass Spectrometry (LC-MS/MS)

Liquid chromatography-mass spectrometry, often abbreviated as LC-MS or HPLC-MS, represents the fusion of mass spectrometry and liquid chromatography techniques. This method, known as LC-MS/MS, holds a predominant position in labs for both qualitative and quantitative analysis of drug substances, drug products, and biological materials. Its widespread use has profoundly influenced the evaluation and comprehension of pharmacokinetic, bioequivalence, and bioavailability data. Compilation of reported analytical methods utilizing LC-MS technique is presented in Table 4 [32-45]. These methods serve as valuable tools for accurate analysis and assessment across various applications within pharmaceutical and biological research.

6. CONCLUSION

This review provides a comprehensive summary of various analytical methods detailed in the literature for determining RDV, SMV, and SFS in bulk, pharmaceutical formulations, and various biological matrices such as blood, plasma and urine with employing spectroscopic, chromatographic, and hyphenated techniques, these methods serve to quantify RDV, SMV, and SFS across different matrices. LC-MS with MS detection proves to be more suitable, providing precise results with minimal effort. Using MS techniques in LC has clear benefits in terms of selectivity and sensitivity. It makes it possible to look at RDV, SMV, and SFS, along with their by-products, in biological samples. Additionally, studies have reported the quantification of these compounds in plasma and other biological fluids using hyphenated techniques like LC-MS, LC-MS/MS, and UPLC-MS/MS. This review not only serves as a valuable resource for further development of analytical methods for this compound trio, but also offers insights into their drug profile, aiding in a better understanding of their analytical assessment.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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