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Review article

A review on analytical profile for newly FDA approved drugs in 2023

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ABSTRACT

In 2023, the field of pharmaceuticals witnessed the approval of several novel drugs by the United States Food and Drug Administration (USFDA). These drugs represent significant advancements in the treatment of various medical conditions and have undergone rigorous evaluation to ensure their safety and efficacy. To support their development and subsequent quality control, a variety of analytical methods have been employed. This review highlights the analytical methods employed for the evaluation and quality control of FDA approved drugs. These methods encompass a range of techniques that enable the characterization, quantification, and quality assessment of pharmaceutical compounds. Commonly employed analytical techniques include chromatographic methods such as high-performance liquid chromatography (HPLC), Liquid Chromatography-Mass Spectrometry (LC-MS), Ultra-Performance Liquid Chromatography (UPLC), Ultra-high-performance liquid chromatography (UHPLC), Ultra-performance liquid chromatography-Mass Spectrometry (UPLC-MS). The Approved Drugs are Bexagliflozin (Sodium-glucose Cotransporter 2 Inhibitor (SGLT2)), Daprodustat (Hypoxia-inducible factor prolyl hydroxylase inhibitor), Valmanasealfa-tycv (Recombinant human lysosomal alpha-mannosidase), Rezafungin(Echinocandin antifungal drug), Sparsentan (Dual endothelin and angiotensin II receptor antagonist), Nirmatrelvir (Anti-viral), Ritonavir (Protease Inhibitors). Overall, the approval of FDA drugs in 2023 relied on the utilization of diverse and robust analytical methods. These methods facilitated the rigorous assessment of drug quality, safety, and efficacy, ensuring that patients receive reliable and effective treatments. The continuous advancement of analytical techniques will further contribute to the development and evaluation of innovative pharmaceuticals in the future.

Keywords: HPLC, LC-MS, UPLC, UHPLC, UPLC-MS.

INTRODUCTION

The U.S. Food and Drug Administration (USFDA) is a federal agency within the United States Department of Health and Human Services. Its primary responsibility is to ensure the safety, effectiveness, and security of various products that are used by the public, particularly in the areas of food, drugs, medical devices, cosmetics, and more. Here's an overview of the USFDA's key functions and responsibilities:

Regulatory Oversight

The USFDA regulates a wide range of products that impact public health. This includes prescription and over-the-counter drugs, vaccines, biologics, medical devices, food and beverages (both human and animal), dietary supplements, cosmetics, and tobacco products.

Drug Approval and Safety

The USFDA reviews and approves new drugs and therapies before they can be marketed to the public. This involves evaluating the safety and efficacy of the products through rigorous clinical trials and scientific research. The agency also monitors the safety of drugs and takes actions if any adverse effects are reported after approval.

Food Safety

The USFDA is responsible for ensuring the safety of the U.S. food supply. This involves regulating food production, distribution, labeling, and packaging. The agency sets standards for food additives and contaminants, monitors foodborne illnesses, and implements recalls when necessary.

Medical Device Regulation

The USFDA regulates medical devices to ensure their safety and effectiveness. This includes items such as pacemakers, imaging equipment, and diagnostic tests. Devices are classified into different categories based on their potential risks, and the regulatory requirements vary accordingly.

Biological Products and Vaccines

The agency oversees the approval and safety of biological products, including vaccines, blood products, and gene therapies. The USFDA ensures that these products are safe and effective before they are made available to the public.

Cosmetics and Personal Care Products

The USFDA regulates cosmetics to ensure that they are safe for consumer use. However, cosmetics are subject to less rigorous testing and regulation compared to drugs and medical devices.

Tobacco Regulation

The USFDA has authority over tobacco products, including cigarettes, smokeless tobacco, and e-cigarettes. The agency aims to reduce tobacco-related illnesses and deaths through regulations, education, and enforcement.

Emergency Response

The USFDA plays a crucial role in responding to public health emergencies such as disease outbreaks, natural disasters, and bioterrorism threats. It coordinates efforts to ensure the safety of the food and medical product supply chains during such crises.

Research and Innovation

The USFDA conducts research to improve its regulatory processes and stay up-to-date with scientific advancements. It collaborates with academic institutions, industry, and other regulatory agencies to enhance its understanding of various products and their effects on public health.

Public Education

The USFDA provides information to the public about health and safety issues related to the products it regulates. This includes educating consumers about making informed choices and understanding product labels.

Overall, the USFDA's mission is to protect and promote public health by ensuring the safety, efficacy, and quality of products that Americans use every day. It employs a combination of regulatory oversight, scientific research, enforcement, and public communication to fulfil its mandate.

High-Performance Liquid Chromatography (HPLC)

HPLC is a powerful analytical technique used for the separation, identification, and quantification of various chemical compounds in a mixture. It is widely employed in diverse fields such as pharmaceuticals, food and beverages, environmental analysis, forensic sciences, and research laboratories. HPLC operates on the principle of chromatography, where a sample mixture is injected into a liquid mobile phase that carries it through a stationary phase packed into a column. The stationary phase consists of porous particles with specific chemical properties that interact differently with the components of the sample mixture. As the sample passes through the column, different compounds separate based on their affinity for the stationary phase [1]. The key components of an HPLC system include a mobile phase solvent reservoir, a pump to deliver the solvent, an injector for sample introduction, a column where the separation occurs, a detector to monitor the eluting compounds, and a data analysis system. HPLC offers a wide range of column choices, including reverse-phase, normal-phase, ion-exchange, size exclusion, and affinity columns, allowing for versatile separation capabilities.

The detector in an HPLC system measures the concentration of the separated compounds and generates a chromatogram, which is a graphical representation of the separation. Commonly used detectors include ultraviolet-visible (UV-Vis) detectors, fluorescence detectors, refractive index detectors, and mass spectrometers. The choice of detector depends on the nature of the compounds being analyzed [2,21]. HPLC offers several advantages, such as high resolution, sensitivity, and versatility. It can separate complex mixtures with multiple components and detect compounds at low concentrations. HPLC methods can be optimized for specific applications, enabling selective and precise analyses. Additionally, HPLC is a relatively fast technique compared to other separation methods like gas chromatography.

Ultra-Performance Liquid Chromatography (UPLC)

UPLC, which stands for Ultra-Performance Liquid Chromatography, is used in various scientific disciplines, particularly in the field of chemistry. It is an advanced form of high-performance liquid chromatography (HPLC) that offers improved resolution, sensitivity, and speed [3]. UPLC utilizes a stationary phase and a mobile phase to separate and analyse complex mixtures of compounds. The stationary phase consists of a packed column with very small particle sizes (typically 1.7 to 2.5 micrometers), which allows for greater efficiency and faster separations compared to traditional HPLC columns. The mobile phase, usually a liquid solvent or a combination of solvents, is pumped through the column at high pressures, typically exceeding 10,000 psi. This high-pressure operation results in increased flow rates and reduced analysis times. The key benefits of UPLC include enhanced resolution, improved peak capacity, and increased sensitivity. With smaller particle sizes, UPLC provides greater surface area for interaction between the sample components and the stationary phase, leading to better separation of closely eluting compounds. The

increased sensitivity allows for the detection and quantification of trace amounts of analytes in complex samples [4]**.** UPLC finds applications in a wide range of industries, including pharmaceuticals, biotechnology, environmental analysis, food and beverage, and forensic science. It is commonly employed for the analysis of small organic molecules, peptides, proteins, amino acids, pesticides, pharmaceutical compounds, and natural products.

Ultra-high-performance liquid chromatography (UHPLC)

UHPLC is an advanced analytical technique used in the field of chemistry and pharmaceutical sciences. It is a highly efficient and powerful form of liquid chromatography that allows for fast and high-resolution separation of complex mixtures. UHPLC has revolutionized the field of chromatography by offering improved performance, sensitivity, and speed compared to conventional high-performance liquid chromatography (HPLC)[5]**.** The key feature of UHPLC is the use of columns packed with small particle sizes (typically 1.8 to 2.5 μm) and high-pressure systems, enabling faster flow rates and increased separation efficiency. The small particle sizes provide a larger surface area for interaction between the analytes and the stationary phase, leading to enhanced separation. Additionally, the high-pressure systems allow for the use of higher flow rates without sacrificing resolution, resulting in faster analysis times and increased sample throughput. UHPLC offers several advantages over traditional HPLC.

The improved resolution and sensitivity make it particularly suitable for the analysis of complex samples, such as biological fluids and natural products. It enables the separation of compounds with similar structures and closely related retention times, which are challenging to resolve using other techniques. The increased speed and efficiency of UHPLC also lead to shorter analysis times, reduced solvent consumption, and improved laboratory productivity [7]**.** The technique finds wide application in various fields, including pharmaceutical analysis, environmental monitoring, food and beverage analysis, forensic science, and bio-analysis. UHPLC is commonly coupled with various detection techniques such as UV-Vis, fluorescence, mass spectrometry, and diode array detectors, allowing for the identification and quantification of analytes with high precision and accuracy.

Liquid Chromatography-Mass Spectrometry (LC-MS)

LC-MS, which stands for Liquid Chromatography-Mass Spectrometry, is widely used in the fields of chemistry, biology, and pharmaceutical sciences. It combines the separation capabilities of liquid chromatography with the detection and identification capabilities of mass spectrometry [7]. In LC-MS, a sample is first introduced into a liquid chromatography system, where it is separated into its individual components based on their physicochemical properties. This separation is achieved by passing the sample through a column packed with a stationary phase, which interacts differently with different components of the sample. As the components elute from the column, they enter the mass spectrometer for detection and analysis. The mass spectrometer in LC-MS measures the mass-to-charge ratio (m/z) of ions generated from the separated components. This information provides valuable insights into the identity, quantity, and structure of the compounds present in the sample. The mass spectrometer also enables the determination of isotopic composition, fragmentation patterns, and even the presence of trace impurities [8]**.**LC-MS has a wide range of applications in various fields. In pharmaceutical sciences, it is used for drug discovery, development, and quality control. LC-MS can accurately quantify drugs and their metabolites in biological samples, aiding in pharmacokinetic studies and therapeutic drug monitoring. It is also employed in environmental analysis to detect and quantify pollutants, such as pesticides and organic contaminants, in water and soil samples.

Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS)

UPLC-MS is a powerful analytical technique used in various scientific disciplines, particularly in the fields of chemistry, biology, pharmacology, and environmental science. It combines two distinct methods, liquid chromatography (LC) and mass spectrometry (MS), to provide high-resolution separation and accurate identification of compounds within complex mixtures.

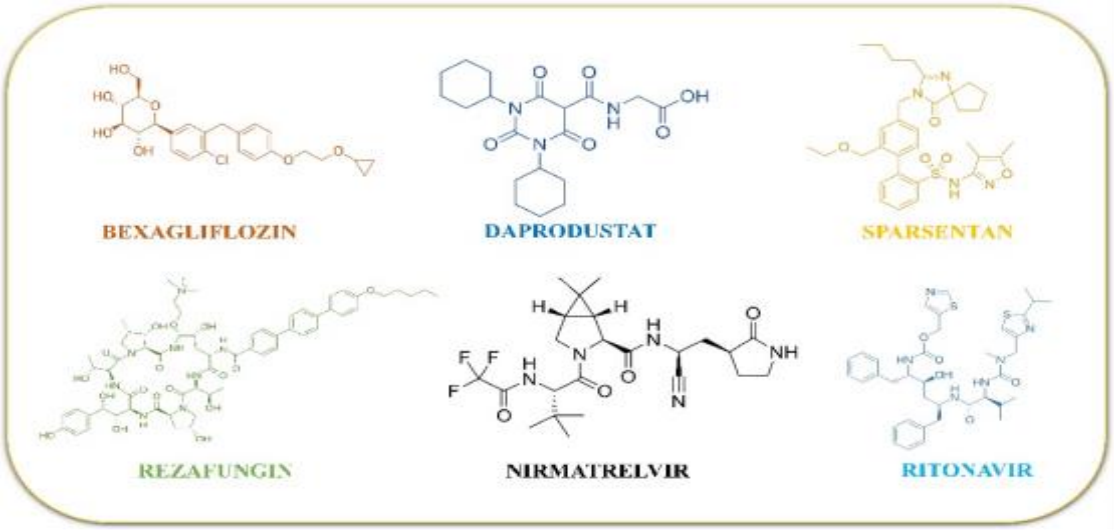
Liquid chromatography is a separation technique that involves passing a liquid sample through a stationary phase, which interacts differently with the various components of the sample, leading to their separation based on their physical and chemical properties. Mass spectrometry, on the other hand, is a technique that measures the mass-to-charge ratio of ions, enabling the determination of molecular masses and the identification of compounds based on their unique mass spectra.

UPLC-MS builds upon traditional high-performance liquid chromatography (HPLC) by using smaller particle sizes in the column packing material and operating at higher pressures. This results in faster separations, improved resolution, and increased sensitivity. The combination of UPLC with mass spectrometry allows for not only precise separation but also highly accurate identification and quantification of compounds, even in complex mixtures at very low concentrations.

The UPLC-MS system consists of three main components: the UPLC system, the mass spectrometer, and the data analysis software. The UPLC system comprises a pump that delivers the sample to the chromatographic column, which separates the compounds, and a detector that records the signals generated. The mass spectrometer then ionizes the separated compounds and measures their mass-to-charge ratios to generate mass spectra. These spectra are subsequently analyzed using specialized software to identify and quantify the compounds present in the sample.

UPLC-MS has diverse applications, including drug discovery and development, metabolomics, proteomics, environmental analysis, food safety testing, and forensic analysis. Its ability to rapidly analyze complex samples with high precision and sensitivity makes it an indispensable tool for researchers and analysts seeking detailed insights into the composition of various samples [10]. Some of the drugs considered for the study are depicted in the figure 1.

Figure 1 Chemical Structures of selected FDA approved drugs in 2023[11]



CONCLUSION

In the year 2023, many drugs were approved by USFDA. In order to develop a pharmaceutical product, new analytical methods have to be developed and validated. The above study presents analytical methods for the estimation of recently approved FDA drugs in API and pharmaceutical dosage forms and biological matrices. Literature survey suggested that different methods like Reverse phase high-performance liquid chromatography (RP-HPLC), Ultra-performance liquid chromatography (UPLC), Ultra-high-performance liquid chromatography (UHPLC), Liquid Chromatography-Mass Spectrometry (LC-MS), Ultra performance liquid chromatography-Mass spectroscopy (UPLC-MS) methods were developed and reported. This makes these methods easy, efficient, precise, accurate, and reproducible to estimate and validate. This review suggests that liquid chromatographic methods are widely used for estimation of selected drugs. This review will help in future to develop the novel analytical methods for the selected approved drugs. Researchers will use this review to develop new methods for further studies on the selected drugs.

Table 1: List of newly approved drugs in 2023[11]

Drug Name	Active Ingredient	Dosage Form	Approval Date	FDA-approved use on approval date*
Sohonos	Palovarotene	Oral Tablet	8/16/2023	To reduce the volume of new heterotopic ossification in adults and pediatric patients (aged 8 years and older for females and 10 years and older for males) with fibrodysplasia ossificans progressiva
Elrexfio	elranatamab-bcmm	Subcutaneous injection	8/14/2023	To treat adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy
Talvey	talquetamab-tgvs	Injection	8/9/2023	To treat adults with relapsed or refractory multiple myeloma who have received at least four prior therapies
Izervay	avacincaptad pegol	Ophthalmic	8/4/2023	To treat geographic atrophy secondary to age-related macular degeneration
Zurzuvae	Zuranolone	Oral	8/4/2023	To treat postpartum depression
Xdemvy	Lotilaner	Ophthalmic	7/25/2023	To treat Demodex blepharitis
Vanflyta	Quizartinib	Oral	7/20/2023	To use as part of a treatment regimen for newly diagnosed acute myeloid leukemia that meets certain criteria
Beyfortus	nirsevimab-alip	Intramuscular injection	7/17/2023	To prevent respiratory syncytial virus (RSV) lower respiratory tract disease
Ngenla	somatrogon-ghla	Subcutaneous injection	6/27/2023	To treat growth failure due to inadequate secretion of endogenous growth hormone
Rystiggo	rozanolixizumab-noli	Subcutaneous injection	6/26/2023	To treat generalized myasthenia gravis in adults who are anti-acetylcholine receptor- or anti-muscle-specific tyrosine kinase antibody-positive
Litfulo	ritlecitinib	Oral capsule	6/23/2023	To treat severely patchy hair loss
Columvi	glofitamab-gxbm	Intravenous infusion	6/15/2023	To treat diffuse large B-cell lymphoma, not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma after two or more lines of systemic therapy

Inpefa	Sotagliflozin	Oral tablet	5/26/2023	To treat heart failure
Posluma	flotufolastat F 18	Intravenous injection	5/25/2023	To use with positron emission tomography imaging in certain patients with prostate cancer
Paxlovid	nirmatrelvir, ritonavir	Tablets, co-packaged for oral use	5/25/2023	To treat mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19
Xacduro	sulbactam, durlobactam	Injection for intravenous infusion	5/23/2023	To treat hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible isolates of Acinetobacter baumannii-calcoaceticus complex
Epkinly	epcoritamab-bysp	Injection, for subcutaneous use	5/19/2023	To treat relapsed or refractory diffuse large B-cell lymphoma (not otherwise specified) and high-grade B-cell lymphoma after two or more lines of systemic therapy
Miebo	perfluorhexyloctane	Ophthalmic solution	5/18/2023	To treat signs and symptoms of dry eye disease
Veozah	fezolinetant	Tablets, for oral use	5/12/2023	To treat moderate to severe hot flashes caused by menopausePress Release
Elfabrio	pegunigalsidase alfa-iwxj	Injection for infusion	5/9/2023	To treat confirmed Fabry disease
Qalsody	tofersen	Intrathecal injection	4/25/2023	To treat amyotrophic lateral sclerosis in adults who have a SOD1 gene mutation
Joenja	leniolisib	Tablets	3/24/2023	To treat activated phosphoinositide 3-kinase delta syndrome
Rezzayo	rezafungin	Powder for injection	3/22/2023	To treat candidemia and invasive candidiasis
Zynyz	retifanlimab-dlwr	Injection	3/22/2023	To treat metastatic or recurrent locally advanced Merkel cell carcinoma
Daybue	trofinetide	Oral solution	3/10/2023	To treat Rett syndrome
Zavzpret	zavegepant	Nasal spray	3/9/2023	To treat migraine
Skyclarys	omaveloxolone	Capsules, for oral use	2/28/2023	To treat Friedrich's ataxia
Filspari	sparsentan	Tablets	2/17/2023	To reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression
Lamzede	velmanase alfa-tycv	Intravenous	2/16/2023	To treat non-central nervous system manifestations of alpha-mannosidosis
Jesduvroq	daprodustat	Tablet	2/1/2023	To treat anemia caused by chronic kidney disease for adults on dialysis for at least four months
Orserdu	elacestrant	Tablet	1/27/2023	To treat estrogen receptor-positive, human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy
Jaypirca	pirtobrutinib	Tablet	1/27/2023	To treat relapsed or refractory mantle cell lymphoma in adults who have had at least two lines of systemic therapy, including a BTK inhibitor
Brenzavvy	bexagliflozin	Tablet	1/20/2023	To improve glycemic control in adults with type 2 diabetes mellitus
Leqembi	lecanemab-irmb	Injection for intravenous use	1/6/2023	To treat Alzheimer's disease

Table 2: Analytical methods for newly approved drugs in 2023

Drug Details	Analytical method	Description of the method	
Brenzavvy (Bexagliflozin) [12]	HPLC	System used	Agilent 1100 liquid chromatographic system
		Column used	CapcellpakC18MG column (100×4.6mm,5 µm, shiseido, Tokyo, Japan
		Mobile phase	Acetonitrile: Methanol: Water:10mM Ammonium acetate (450:275:275:5.5 v/v/v/v)
		Flow rate	0.7 mL/min
		Injection volume	10 µL
		MS detection technique employed	API 4000 triple quadrupole mass spectrometer
	LC- MS/MS	System used	Shimadzu LC – 20A liquid chromatography system
		Column used	Waters Nova- pak C18 (150×3.9mm,4µm) column
		Mobile phase	A :0.1% formic acid in 0.5mM NH4 Ac under positive mode and 5mM NH4Ac under negative mode B : 0.1% formic acid in mixture of acetonitrile /methanol (50/50) The fraction of A was 85% to 2min ,50% to 4.5 min and 15% to 5.6 min, thereafter 85% to 8 min
		Flow rate	0.8 mL /min
		Injection volume	10 µL
		Mass spectrometric detection	API 4000 LC – MS/MS Mass spectrometer

		technique employed	
		Column temperature	250C
	UPLC	System used	UPLC-Q/TOF MS system for analysis on a waters ACQUITY UPLC system (water corporation, Milford, MA)
		Column used	ACQUITY HSS T3 C18 column with 1.7 µm particle size (100×2.1mm)
		Mobile phase	A: 10 mM Ammonium acetate B: Acetonitrile with 0.05% formic acid
		Flow rate	0.5mL /min
		Injection volume	10 µL
		Run time	20 min
		Detection technique	Synapt Q- TOF MS
		Column temperature	400C
Jesduvroq (Daprodustat)	UPLC-MS [13]	System used	A waters (Milford, MA, USA) Acquity 1-class UPLC system
		Column used	SupelcoAscentis C18 column (150×2.1mm,2.7µm) (sigma - Aldrich,Milano, Italy)
		Mobile phase	Ultra -purified water (eluent A) and Acetonitrile (eluent B),both containing 0.1% of formic acid
		Flow rate	250 µL/min
		Injection volume	10 µL
		Detection technique	Triple quadrupole (or) orbit rap
		Column temperature	300C
	UHPLC[14]	System used	Vanquish UHPLC system
		Column used	ACQUITY UPLC BEH C18 (100mm× 2.1mm ID, 1.7µm; waters)
		Mobile phase	Solvent – A (0.1%v/v formic acid in water) Solvent-B Acetonitrile (gradient elution)
		Flow rate	0.6 mL /min
		Injection volume	2 µL
		Maximum injection time	50 ms
		Column temperature	400C
Lamzede (Valmanase alfa tycv)	LC-MS/MS[15]	System used	Liquid chromatography
		Column used	NH2 column(Luna 3micrometres,100A,50mm× 2.1mm (Torrence,USA),40oC
		Mobile phase	Solvent A-Formic acid 0.2% v/v in water. SolventB-Formic acid 0.2%v/v in acetone nitrile (elution gradient)
		Flow rate	400 µL/ min
		Injection volume	10 µL
		Detection	Agilent 6410 Triple quadrutle
Rezzayo (Rezafungin)	LC-MS/MS[16]	System used	Liquid chromatography
		Column used	dc18,2.1×50mm, 5 µm
		Mobile phase	0.1% formic acid in water /0.1% formic acid in acetonitrile or tetrahydrofuran
		Detection	API 4000 mass spectrometer
	HPLC[17]	System used	Agilent 1260 HPLC system
		Column used	C18(250×4.6mm, 5 µm)
		Mobile phase	A-0.057 mol/L of sodium by hydrogen phosphate, 0.014 mol/L sodium dodecyl sulphate B - Acetonitrile
		Detection Wavelength	230 nm
		Flow rate	1mL/ min
		Injection volume	5 µL
Filspari (Sparsentan)	LC-MS/MS[18]	System used	Validated Liquid chromatography
		Column used	Atlantis d18 (3 µm, 2.1 × 50 mm; Waters)
		Mobile phase	A-5mM Ammonium acetate in water B- Acetonitrile C- H2O: MeCN (50:50 v/v)
		Detection technique	Tandem Mass spectroscopy
		Flow rate	0.5 mL/min (pump C=0.3 mL/min)
		Calibration range	2 to 4000 ng /mL
		Lower limit of quantitation	2 ng /mL
Paxlovid (Nirmaterelvir & Ritonavir)	HPLC[19]	System used	Efficient Chromatographic Separation system
		Column used	BDS HypersilC18 [250×4.6mm,5 µm particle size]
		Mobile phase	Ethanol; water[80: 20% v/v]
		Flow rate	1 mL/min
		Retention time	Nirmatrelvir-4.9 min Retonovir-6.8 min

		Linearity	1.0–20.0 µg/mL
		Injection volume	20 µL
		Detection	UV Detection 250 nm
	RP-HPLC [20]	System used	RP-HPLC Chromatographic system
		Column used	Dikmaspursil C18 column (4.6×150mm, 3 µm)
		Mobile phase	0.1% formic acid: acetonitrile (65:35% v/v)
		Flow rate	1 mL /min
		Wavelength	253 nm
		Detector	PDA detector

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