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Review Article

RECENT METHOD DEVELOPMENT BY ANALYTICAL TECHNIQUES OF NEW FDA APPROVED DRUGS IN 2021

ISHVARCHANDRA PARMAR, YOGI A PATEL[1]

Department of Pharmaceutical Chemistry, [1]Department of Quality Assurance, S. S. R. College of Pharmacy, S. S. R. Campus, Sayli Road, Silvassa 396230, Dadra and Nagar Haveli, India
Email: ijparmar2266@gmail.com

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ABSTRACT

In this present situation increase in the number of diseases has been observed and several new medications are invented and have been developed to treat various disorders, which are approved by FDA. But before these drugs come to market it must undergo several procedures. The validation and analytical process of a new drug development helps in ensuring its purity and reliability. This process involves the use of various analytical techniques to collect data about the drug. This review includes various types of analytical techniques such as ultraviolet-visible spectrophotometric and some chromatography methods (High-performance thin-layer chromatography, High-performance liquid chromatography, gas chromatography), hyphenation techniques such as LC-MS of the newly approved drug in the year of 2021 have been discussed.

Keywords: Analytical method, FDA approved drugs, HPLC, UV-VIS, HPTLC, LC-MS

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INTRODUCTION

The development of an analytical method and validation are key parameters for discovering, developing and manufacturing of pharmaceutical substances. Method development could be a procedure of validating that an analytical method is appropriate to be used to live the concentration of an API in an exceedingly pharmaceutical dosage form as the amount of medicine that is launched into the market each year is rising. This drug can either be newly formulated or structurally modified of the main drug. Under these conditions, analytical procedures and standard methods of this latest medications might not be mentioned in the pharmacopoeias [1]. So, the development of analytical methods is necessary for such new approved drugs. Internal control laboratories use official test procedure for ensuring the identity, purity, and efficiency including the performance of drug products. To analyse the analyte there are several methods such UV Spectrophotometric, Ultra Performance liquid chromatography, High-performance thin-layer chromatography, High-performance liquid chromatography, Stability indicating High-performance liquid chromatography, LC-MS, Spectro-fluorimetry, GC-MS, etc. [2]. In the Pharmaceutical industry Qualitative and Quantitative determination of medicine, API, Raw materials, and biological samples, there are Analytical methods used like spectrometry and chromatography. These methods accustomed the identity, purity, potency and performance of medicine [3]. Analytical method development plays the most roles within the expansion in manufacture of pharmaceuticals.

The Food and Drug Administration (FDA) is a national government specialized agency of the United States. It was established in 1906 as the Department of Health and Human Services.

FDA

This organization mainly takes responsibility for governing and managing the safety of food, dietary supplements, therapeutic medications, vaccine, biological medicinal product and medical devices such as radiation-emitting devices, blood products, veterinary products and cosmetics.

Headquarters of FDA is situated in oak, Maryland. This organization controls 223 fields offices and Research Laboratories which are located across the 50different states.

In 2008, the FDA initiated for introducing its offices in other nations which include India, China, the United kingdom and Costa Rica Belgium.

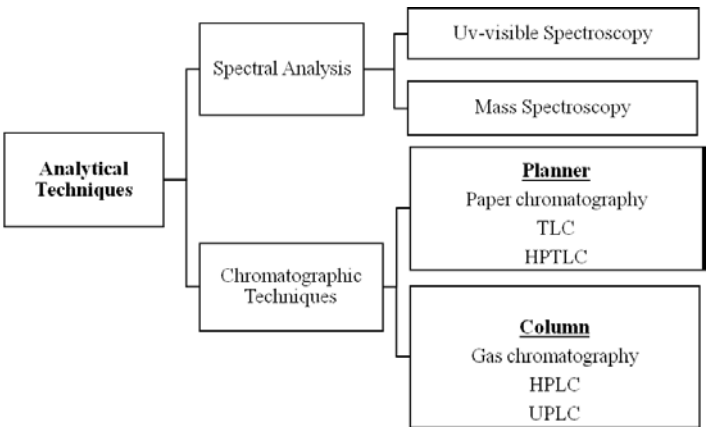

Fig. 1: Flowchart of analytical techniques

UV spectrophotometric

The UV-Visible spectrometry is considered as most traditional instrumental system for analysis and it is finest methods used for determining analytes which are present in sample and in micro and semi micro amounts. It is concerned with detection of the effects of electromagnetic radiation interacting with absorbing entities such as atoms, molecules, or ions in the UV and/or visible spectrum [4]. It is useful for analyzing various substances such as biomolecular, inorganic and organic compounds. Results of this analytes are used for research purpose, industry, clinical trial laboratories, it is also helpful for environmental samples. Therefore, it is necessary to learn about the origin of the UV-VIS spectrum and its characteristics.

HPLC

High-Performance Liquid chromatography (HPLC) is that leading distinctive separating instrument which is used for many aspects of drug manufacture and analysis. As HPLC is highly sensitivity and specific, it gives précised result. But, HPLC is widely used mainly for two reasons firstly Qualitative and analysis of unknown mixtures and secondly, Mixture's separation for the later analysis. The separation mode depends totally on interacting relationship between the analyte, stationary Phase, mobile Phase [5].

HPTLC

In modern era, The High-performance thin-layer chromatography an evolved system of thin layer chromatography with superior separation functioning and detection limits than GC and HPLC. As it is an easily adaptable analytical method that may be used for either qualitative or quantitative applications. Separation takes place due to adsorption and partition, or each, depending on the form of adsorbents used on the plates and the development solvent system [6].

LC/MS-MS

The Liquid chromatography-Mass spectrometry is considered as most potent analytical process which is sensitive and specific. The LC-MS is hyphenated analytical System which works in combination of two system, liquid-Chromatography(LC)and mass spectrometry (MS) [7]. Via passing throughout column the components of mixtures get separated in HPLC (LC), but this LC cannot differentiate the separated component so, Mass spectrometry helps to identify unknown substances and recognize and also useful to elucidate their structures. As, spectrum mixture is highly complicated because of overlapping spectra, Mass spectrometry individually isn't helpful for identifying mixtures. Hence, they are used in combination for more accurate result. Therefore, it is possible to separate and determine relative atomic masses or molecule masses at the same time [8].

Table 1: Different analytical methods of newly approved drug in 2021

S. No.	Brand name	API	Analytical method	Description of the method	Reference
1	Cabenuva	Cabotegravir and rilpivirine	RP-UPLC	**System-**Waters Acquity UPLC **Column-**Azilent C_{18}(150*4.6 mm) **Mobile Phase-**orthophosphoric acid (60): acetonitrile (40) **Wavelength-**245 nm **Flow rate-**1 ml per min **Injection volume-**10 ml **Linearity-**25-150µg/ml **Total run time-**6 min	[9]
			HPLC-MS	**System-**HPLC system Waters Alliance LC (model 2695) **Column-**Symmetry C_{18} (4.6 mm150 mm, 3.5µ) **Mobile Phase-**0.1% HCOOH: ACN (80:20) **Wavelength-**231 nm **Flow rate-**1 ml/min **Injection volume-**10 ml **Retention time-**Cabotegravir-2.050 minRilpivirine-3.942 min **Linearity-**Cabotegravir-20-300 g/ml Rilpivirine-30-450 g/ml **Total run time-**5 min	[10]
2	Lupkynis	Voclosporin	LC/MS/MS	**System-**HPLC Applied Biosystems/MDS-Sciex API3000 Turbo Ion Spray (TIS) **Column-**Zorbax SB $C_{8,}$(2.1 mm12.5 mm) **Mobile Phase-**0.02% (GAA) glacial acetic acid: 0.02 mmol sodium acetate **Injection volume-**20 ml **LLOQ-**1–200 ng/ml **Total run time-**2 min **Mass spectrometric detection-**Mode-positive ionization multiple reaction monitoring (MRM)m/z 1236.8→1112.8	[11]
3	Cosela	Trilacicilib	HPLC	**System-**e-2695 chromatographic system **Column-**ODS Inertsil (150 mm4.6 mm, 3.5 µ) **Mobile Phase-**(50)ACN: (50) 0.1% ortho phosphoric acid **Wavelength-**220 nm **Flow rate-**1 ml/min **Injection volume-**10 ml **Retention time-**4.358 min. **Linearity-**3-45 µg/ml **Total run time-**6 min	[12]
4	Fotivda	Tivozanib	RP-HPLC	**System-**Waters alliance liquid chromatography (model 2695) **Column-**X~Bridge phenyl, (150 mm4.6 mm, 3.5 µ) **Mobile Phase-**ACN: 0.1 % HCOOH (50/50) **Wavelength-**216 nm **Flow rate-**1 ml/min. **Retention time-**4.07 min **Linearity-**1.34-20.1µg/ml	[13]
			LC-MS	**System-**Acquity UPLC, Nexera 2 series LC system connected	[14]

S. No.	Brand name	API	Analytical method	Description of the method	Reference
				(TQ-MS) triple quadrupole mass spectrometer API4000 (Sciex) **Column-**BEH C_{18} (50 mm2.1 mm, 1.7 µm) **Mobile Phase-**0.1% HCOOH in H_2O: 0.1% HCOOH in ACN **Flow rate-**0.3 ml/min **Injection volume-**2 µl **Retention time-**1.35 min **Linearity-**0.5–5000 ng/ml **Total run time-**15 min **Mass spectrometric detection-** m/z 455 to 341, m/z 456 to 341	
5	Qelbree	Viloxazine	HPLC DAD	**System-**HPLC-DAD **Column-**Nucleosil RP-18 (250 mm 4.6 mm, 5 mm) **Mobile Phase-**(pH 3.8) Buffer 20 mmol phosphate: ACN **Wavelength-**220 nm **Flow rate-**1 ml/min **Linearity-**7-45 µg/ml	[15]
6	Nextstellis	Drospirenone and estetrol	RP-UPLC	**System-**Waters Acquity UPLC system PDA detector **Column-**Luna C_{18} (100 mm 2.6 mm,1.6 µ) **Mobile Phase-**acetonitrile: 0.1% formic acid (70:30) **Wavelength-**262 nm **Flow rate-**1 ml/min **Injection volume-**10 ml **Retention time-**drospirenone-0.989 min E4-1.878 min **Linearity-**Drospirenone =3-45 µg/ml E4 =14.2-213 µg/ml **Total run time-**3 min	[16]
7	Lumakras	Sotorasib	RP-HPLC	**System-**Waters alliance liquid chromatography (model 2695) **Column-**symmetry C_{18}(150 mm4.6 mm, 3.5µ) **Mobile Phase-**(70) Acetonitrile: 0.1% OPA (30) **Wavelength-**221 nm **Flow rate-**1 ml/min **Retention time-**2.271 min **Linearity-**10-150µg/ml	[17]
			LC MS (Mouse plasma and Tissue homogenates)	**System-**Acquity UPLC® Shimadzu Nexera X2 (TQ/MS) triple quadrupole mass spectrometer (TIS)Turbo Ion Spray® **Column-**BEH C_{18} (dp.1.7 µm, 30 mm2.1 mm) prefilter (2.1 mm, 0.2 µm) **Mobile phase-**methanol: 0.1% HCOOH in water (50:50) **Flow rate-**0.6 ml/min **Injection volume-**2 ml **Retention time-**0.5 min **Linearity-**2–2,000 ng/ml **Mass spectrometric detection-**positive (ESI) electrospray ionization (SRM) Mode-selected reaction monitoring m/z 561.2 → 134.0	[18]
			LC/MS-MS (Mice)	**System-**Shimadzu UFLC Prominence connected with Sciex 5500 triple quadrupole mass spectrometer **Column-**Atlantis d C_{18} (5 µm,50 mm 4.6 mm) **Mobile Phase-**0.2% HCOOH: ACN (25/75) **Flow rate-**0.65 ml/min **Retention time-**0.95 min **LLOQ-**1.08 ng/ml **Total run time-**2 min **Mass spectrometric detection-** Mode-multiple reaction mode (MRM) (ESI) positive electro sprayionization) m/z 561.1→134.1 and 566.5→98.2	[19]
8	Truseltiq	Infigratinib	LC MS/MS	**System-**Agilent (1200) (TQ)Triple Quadrupole (6410) **Column-**Agilent ZORBAX SB-C_8 (1.8 µm,30*2.1 mm) **Mobile Phase-**(20%) 0.1 percent formic acid in water: (80%)ACN **Flow rate-**0.2 ml/min **Injection volume-**5 ml **Retention time-**1.54 min **Linearity-**05–500 ng/ml **Total run time-**2 min **Mass spectrometric detection-**positive ion source electrospray ionization (ESI) Mode-multiple reaction monitoring (MRM)m/z 561 → 339	[20]
9	Kerendia	Finerenone	HPLC-MS/MS	**System-**e Milli Q system **Column-**Luna C_{18}(20 *2 mm, 3 µm)	[21]

S. No.	Brand name	API	Analytical method	Description of the method	Reference
				Mobile Phase-ACN: 0.01 mol/l ammonium acetate (80:20 v/v) **Flow rate-**1 ml per min **Injection volume-**15 ml **Retention time-**3.8 min **LLOQ-**0.100 µg/l-200 µg/l **Mass spectrometric detection-** MRM, multiple reaction monitoring; m/z 379.05/217.90	
10	Fexinidazole	Fexinidazole	UPLC MS/MS	**System-**Acquity UPLC system **Column-**C_{18}(1.7 µm,2.1 mm50 mm) **Mobile Phase-**0.1% HCOOH: ACN **Flow rate-**0.6 ml/min. **Injection volume-**5 ml	[22]
11	Exkivity	Mobocertinib	LC-MS/MS	**Column-**ODS-3 column (i. d; 5 µm,50 mm4.6 mm) **Mobile Phase-**A Mixture of water with 0.1% HCOOH: methanol **Flow rate-**0.5 ml/min. **Linearity-**1-1000 ng/ml **Mass spectrometric detection-** Mode-Selected reaction monitoring (SRM) Positive ion source electrospray ionization (ESI), m/z 587.01 → 71.88	[23]
			HPLC	**System**-e-2695 chromatographic **Column-**X-bridge phenyl column (150 mm x 4.6 mm, 3.5 µ) **Mobile phase-**Acetonitrile: 0.1% o-phosphoric acid (OPA) (60:40 v/v) **Flow rate-**1 ml/min**Wavelength-**224 nm **Injection volume**-10 ml **Retention time-**2.271 min **Linearity-**6-90 µg/ml	[24]

Table 2: List of no reported analytical methods of newly approved drug in 2021

S. No.	Brand name	API	Manufacturing company
1	Verquvo	Vericiguat	Merck and Co., Inc.
2	Tepmetko	Tepotinib	EMD Serono, Inc.
3	Ukoniq	Umbralisib	Rhizen Pharmaceuticals
4	Evkeeza	evinacumab-dgnb	Regeneron Pharmaceuticals, Inc
5	Amondys 45	Casimersen	Sarepta Therapeutics, Inc
6	Nulibry	Fosdenopterin	BridgeBio Pharma, Inc
7	Pepaxto	melphalan flufenamide	Oncopeptides Inc
8	Azstarys	serdexmethylphenidate and dexmethylphenidate	Corium, Inc.
9	Ponvory	ponesimod	Janssen Pharmaceuticals, Inc.,
10	Zegalogue	dasiglucagon	Beta Bionics, Inc.,
11	Jemperli	dostarlimab-gxly	Glaxo Smith Kline LLC.
12	Zynlonta	loncastuximab tesirine-lpyl	Avid Bioservices, Inc.
13	Empaveli	Pegcetacoplan	Apellis Pharmaceuticals, Inc.
14	Rybrevant	amivantamab-vmjw	Janssen Biotech, Inc.,
15	Pylarify	piflufolastat F18	Progenics Pharmaceuticals, Inc
16	Lybalvi	olanzapine and samidorphan	Alkermes, Inc.
17	Brexafemme	ibrexafungerp	SCYNEXIS, Inc.
18	Aduhelm	aducanumab-avwa	Biogen MA, Inc.,
19	Rylaze	asparaginase erwinia chrysanthemi (recombinant)-rywn	Rylaze, Jazz, Pharmaceuticals, Inc
20	Rezurock	Belumosudil	Surface Logix, Inc
21	Bylvay	Odevixibat	Albireo Pharma, Inc.
22	Saphnelo	anifrolumab-fnia	AstraZeneca
23	Nexviazyme	avalglucosidase alfa-ngpt	Genzyme Corporation,
24	Welireg	Belzutifan	Peloton Therapeutics
25	Korsuva	Difelikefalin	Cara Therapeutics, Inc.
26	Skytrofa	lonapegsomatropin-tcgd	Ascendis Pharma, Inc
27	Tivdak	tisotumab vedotin-tftv	Seagen Inc.
28	Qulipta	Atogepant	AbbVie Inc.,
29	Livmarli	Maralixibat	Mirum Pharmaceuticals, Inc
30	Tavneos	Avacopan	ChemoCentryx, Inc.,
31	Scemblix	Asciminib	Novartis
32	Besremi	ropeginterferon alfa-2b-njft	PharmaEssentia Corporation
33	Voxzogo	Vosoritide	BioMarin Pharmaceutical Inc.
34	Livtencity	Maribavir	Takeda Pharmaceuticals USA Inc
35	Cytalux	Pafolacianine	On Target Laboratories, Inc
36	Tezspire	tezepelumab-ekko	Amgen, Inc.
37	Vyvgart	efgartigimod alfa-fcab	argenx SE
38	Leqvio	Inclisiran	Novartis AG
39	Adbry	tralokinumab-ldrm	LEO Pharma Inc

CONCLUSION

The development of the new method and validation of analytical methods is an essential step for developing of any pharmaceutical products. This review represents that many drugs been approved in the year of 2021, for use in market and based on the literature review it can be concluded that table 1 and table 2 drugs individually or its combination with another drug spectroscopy and chromatography methods are accessible and other remaining newly approved drugs there has been no spectroscopy or other information available. Although, many validation parameters of particular drugs have already reported, it is concluded that various analytical techniques like spectrophotometric, HPTLC, HPLC, GC-MS and LC-MS can be further developed for these formulations with the variations. It is vast opportunity for the development of new methods for newly approved drugs, as there is no well-established technique for some newly approved drugs or their combination with other drugs.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors hereby declare that there is no any conflict of interest involved in this paper.

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